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TUMORS OF TENDON SHEATHS, JOINT CAPSULES AND MULTIPLE XANTHOMA

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I. TUMORS OF THE TENDON SHEATHS

Many variants of sarcoma have always been recognized, especially according to the structure, i. e., the cell formation. From the cell formation, much information can often be obtained about the prognosis, and this, of course, is the important question. One must proceed, however, with great caution, for the prognosis may be favorable, even when the number of cells is great, and the tumor histologically must be interpreted as sarcoma. As an example may be mentioned the altered view in recent years concerning certain giant cell sarcomas in the osseous system, which were formerly regarded and treated as ordinary sarcomas but which are now given a good prognosis; consequently the treatment has become more conservative, that is to say, minor operative interventions may be permitted. Here, also, one must be cautious and not change the standpoint too hastily.

The localization itself, however, is often of prognostic significance. This is the case with tumors that are regarded as arising from the tendon sheaths and that form a more or less well defined group of "sarcoma." More than three decades have passed since French authors—Heurtaux, Dor—first distinguished them as a separate group and enumerated their most important characteristics: their peculiar structure with numerous and variable cell forms, including many giant cells, the numerous large young fat cells—xanthoma cells—and the abundant hemosiderin. Subsequently, the frequent and striking content of cholesterol esters in large vesicular cells ("Schaumzellen") was recognized, causing these tumors to be classed with xanthoma and "xanthelasma" and even to be considered as connected with abnormalities in the metabolism of cholesterol.

In Scandinavian literature the subject has, so far as I know, been dealt with only by Ali Krogius,¹ who described four cases of solitary

1. Krogius, Ali: Finska läk.-sällsk. handl. 64:102, 1922.

tumors and one case of multiple xanthoma in a child. A number of such tumors have been seen at this institute during the last six or seven years, and I have found it worth while to describe them briefly. I have investigated eleven tumors from tendon sheaths. The point of origin is, however, not always easy to determine. It can be ascertained most definitely when the tumor is in immediate connection with a sheath, whereas the point of origin is far less certain in case the tumor is outside or in the vicinity of a joint, covered with skin and without immediate connection with either a tendon sheath or a joint capsule. It may then be almost impossible to say anything certain about the point of origin, and it may be especially difficult to preclude the possibility of the tumor arising from the subcutaneous connective tissue.

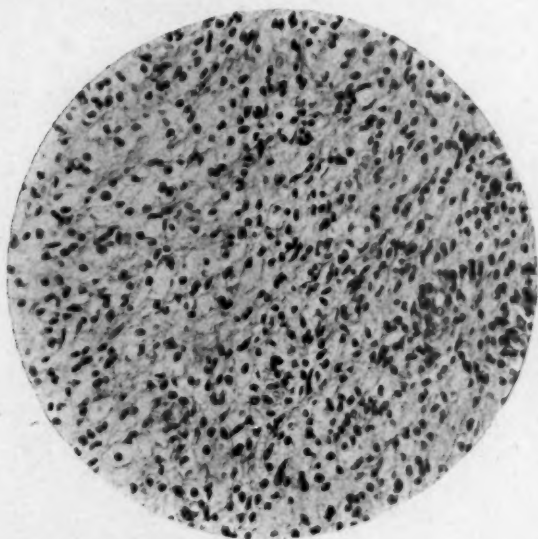


Fig. 1 (case 1).—Polymorphocell sarcoma (or cellular fibroma?) with giant cells and xanthomatous parts; $\times 220$.

REPORTS OF CASES

CASE 1.—A woman, aged 67, presented a tumor on the volar side of the second joint of the fourth finger. She said that she had noticed the tumor two years before, when it was the size of a bean. It remained unchanged for one and a half years, and afterward grew rapidly. The skin was free over the tumor, while the sheath of the flexor tendon seemed to be infiltrated. The growth was not connected with the periosteum. The tumor was flat, about the size of a Spanish nut, fairly well outlined, movable and bounded in places by a capsule of connective tissue. Most of it was fairly hard; parts were soft, and it consisted of gray-white tissue, with here and there yellowish or yellowish brown spots and patches. Microscopically, its structure was variable and cellular, mainly composed of small, closely packed cells of the nature of connective tissue cells with small, round or oval nuclei and a distinct intercellular substance (fig. 1). Here and there, especially toward the surface under the capsule, were islands of

giant cells, of medium size, usually round, with numerous nuclei, sometimes central and sometimes peripheral, arranged in rings. Scattered islands of large, transparent vesicular cells with small, as a rule central, nuclei occurred (fig. 2). These cells were sharply outlined and polygonal, resembling epithelium. The protoplasm was scanty and transparent, as if the contents had dissolved; in other words, there were fat cells. There seemed to be all possible transitions, from the small, connective-tissue-like cells (even in the sarcomatous parts) to the large vesicular cells. The fatty tissue sometimes formed sharply defined clusters, sometimes long strips, which merged into the other parts. Some of the cells contained a little yellow-brown pigment; large masses of pigment were not found. In parts of the stroma there was fibrillation or hyaline swelling and degeneration, with necrosis and cystlike cavities in some places.

The tumor was deemed to be a polymorphocellular sarcoma (or cellular fibroma?), with giant cells and xanthomatous parts. It did not recur.

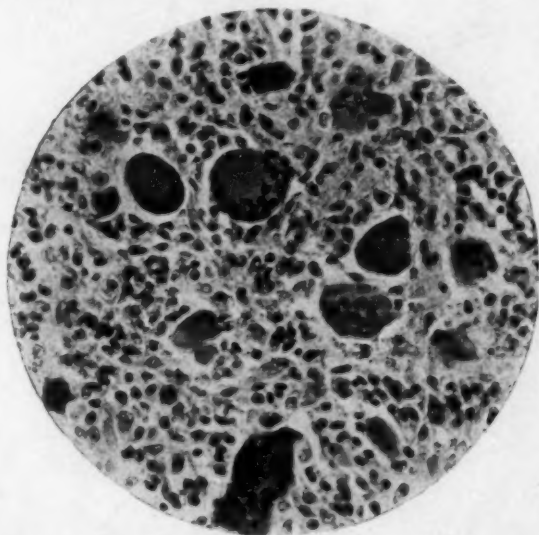


Fig. 2 (case 1).—Polymorphocell sarcoma (or cellular fibroma?) with giant cells and xanthomatous parts; $\times 220$.

CASE 2.—A tumor from the flexor tendon of the little finger in a woman, aged 32, had developed in the course of two years, with rapid growth in the last year. It was adherent to the tendon sheath, but not to the periosteum, and was fairly firm and as large as a Spanish nut; the surface was uneven and nodular, gray-white and compact, with indistinct stripes and yellow patches.

Microscopically, the tissue was rich in cells, round, oval, spindle-shaped and polymorphic. Giant cells were also present, with abundant protoplasm and numerous nuclei. Pigment was not found. The stroma was fairly abundant, and most of it was fibrillary; parts were hyaline and somewhat swollen. In a few places, vesicular cells with sharp outlines resembling young fat cells (xanthomatous tissue) were observed.

The tumor was regarded as a rather benign xanthofibroma giganto-cellulare (sarcoma?).

CASE 3.—A woman, aged 70, had a tumor the size of a walnut, lobate, rather soft and tender to touch under the skin of the ball of the little finger and connected with the fascia. Microscopically, the structure resembled most spindle cell sarcomas, with small, fairly variable cells. After a year the growth recurred, and two similar masses were removed. This was four years ago, and there has not been any further recurrence.

CASE 4.—In a woman, aged 56, a "xanthosarcoma" developed, in the course of five years, on the lateral side of the first joint of the left middle finger. Growth was rapid in the last six months. The tumor was larger than a walnut, with offshoots to the volar side, as well as in between the third and fourth metacarpal bones (fig. 3). The size was 4 by 2 cm. The growth adhered to the tendon sheaths of the flexor muscles, and in places to the extensor muscles, with

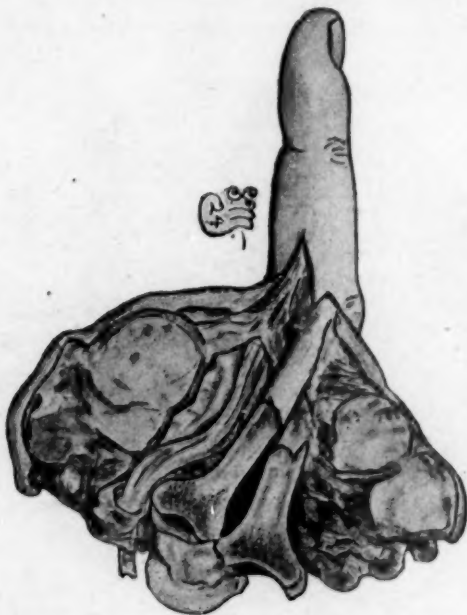


Fig. 3 (case 4).—Giant cell xanthosarcoma adherent to tendon sheaths, muscles and periosteum of first phalanx of left middle finger.

prolongation under and between the tendons and also to the periosteum of the first phalanx, where the bone was eroded. The consistency was soft, and the color a peculiar yellow, ochre-yellow, in parts brownish yellow and in others brownish black.

From its structure, the tumor must be regarded as most probably a "sarcoma xanthomatosum giganto-cellulare," but it was comparatively poor in cells (fig. 4). As the tumor had developed slowly during a number of years, it was doubtless comparatively benign. Recurrence did not take place.

CASE 5.—In a man, aged 52, two hard nodules, one as large as a pea and one a little smaller, formed in the sheath of the flexor tendon on the little finger of the left hand, possibly as a result of the pressure of the strap of a heavy drilling machine. Microscopically, the structure resembled that of a giant cell fibrosarcoma (fibroma?).

CASE 6.—In a man, aged 45, a tumor, the size of a walnut, developed in the course of two years in the sheath of the flexor of the thumb. It was hard, firm, nodular, gray-yellow and traversed by fibrous stripes. The structure was similar to that in case 5, but with abundant pigment. Recurrence had not taken place after four years.

CASE 7.—A woman, aged 40, presented a tumor, the size of a hazelnut, slightly nodular, gray-brown, of elastic consistency and the same structure as the growths in cases 5 and 6, which had developed in the course of two years on the tendon sheath of the index finger on the side toward the hand.

CASE 8.—A man, aged 53, had had a tumor on the foot behind the internal malleolus for twenty-five years. Rapid growth developed after a blow on the tumor. When removed, it was the size of a hen's egg, and was firm, fibrous, traversed by hemorrhages, lobar, gray-white and not connected with the skin, but infiltrating the sheaths and the tendons themselves. In structure it resembled

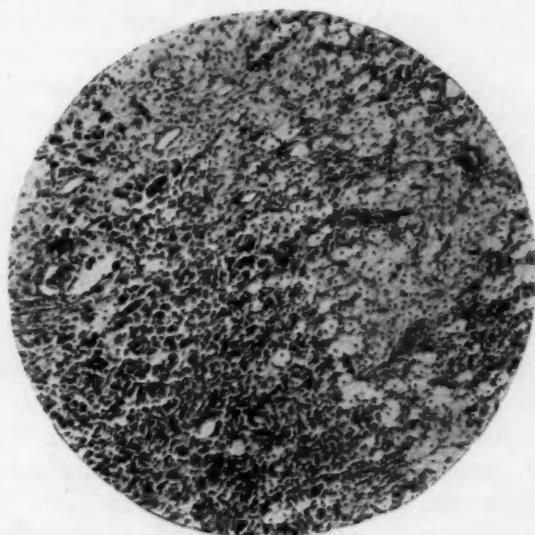


Fig. 4.—Microscopic section of tumor shown in figure 3; $\times 100$.

a spindle cell or polymorphocell sarcoma. Some hyaline as well as cartilaginous and osteoid tissue was present; giant cells were observed. The growth soon recurred, and the foot was amputated three months later. A new, egg-sized tumor was then found under the skin toward and along the achilles tendon. This growth contained a number of giant cells.

CASE 9.—In the course of three or four years there developed on the basal phalanx of the right little finger of a man, aged 40, a firm, hard tumor the size of an almond, which adhered to the tendon sheath and to the periosteum. It was easy to remove. The patient was an ardent card player and would strike his finger against the table just at the spot where the tumor developed. The structure was that of fibrosarcoma without giant or xanthoma cells.

CASE 10.—In the course of three years a tumor developed on the volar surface of the left hand, on a level with the capitulum of the fourth metacarpal, and adherent to the tendon sheath; it was the size of a Spanish nut, hard, nodular and yellowish. Microscopically, it proved to be sarcoma fuso-giganto-cellulare.

CASE 11.—In the course of about two years, a tumor grew to the size of a hazelnut on the thumb of a woman, aged 23; it was gray-white to yellow-white, was sharply outlined and arose from a tendon sheath. Microscopically, it proved to be sarcoma fuso-giganto-cellulare pigmentosum.

The tumors of the sheaths of tendons are characterized by lobate structure, sharp demarcation and soft consistency. Sometimes they are intensely yellow, at times with red-brown patches. They are located especially on the tendons of the upper extremities, and first and foremost on the flexor tendons of the hands and fingers; more seldom they occur on the feet and toes, or around the ankle joints. They occur usually in the second, third or fourth decades, and sometimes develop after trauma (case 5 and especially case 9).

According to the classification of Tourneaux,² in ninety-three cases the tumors occurred on the fingers forty-eight times, on the hands twelve times, on the forearm six times, on the toes seven times, on other places on the foot nineteen times and on the legs once. According to Spies'³ classification of tumors in the tendon sheaths and aponeuroses, tumors were found twenty-one times on the right hand, sixteen times on the left hand, thirty-two times on the under side of the fingers and the vola manus and eight times on the dorsal side. He himself described five cases, three on the fingers, one on the hand and one on the leg. Of Krogus' four cases, one was on the hand, one on the dorsal side of the finger, one on the foot and one on the leg.

My series comprises eleven cases, of which ten were in the upper extremities and one on the foot (case 8). Most of the tumors were situated on the flexor tendons of the fingers (cases 1, 2, 4, 5, 6 and 7), while in case 9 the growth was on the extensor side. In cases 3 and 10 the tumor was on the wrist. As a rule, it is said that there is not any difference between the two sexes as regards frequency. Most of the tumors in my patients were in women (six) and usually in persons over 40 years of age. Often there was a slow growth extending over five, ten or twenty years (cases 4 and 8). The tumors seldom became larger than a hazelnut or walnut. As a rule, they were benign, and in most cases did not occasion metastasis. Metastasis was observed six times in Tourneaux's series. Recurrence after removal, on the other hand, is more frequent (cases 3 and 8).

The structure is remarkable, with fat tissue of a peculiar kind—"xanthoma tissue"—as well as numerous giant cells and pigment. My cases show, however, that none of the characteristics generally assigned to these tumors are constant in all, as Krogus maintains. The main substance consists of a cellular tissue with cells of the connective tissue

2. Tourneaux: *Rev. de chir.* **47**:817, 1913.

3. Spies: *Frankfurt. Ztschr. f. Path.* **13**:1, 1913.

type, and the usual microscopic diagnosis is sarcoma. But, in addition, giant cells often occur, sometimes in large numbers.

"Xanthoma tissue" was found in cases 1, 2 and 4, sometimes in such quantity that the fat-containing portions dominated the picture. Pigment in large quantities was found less frequently. The fat tissue had the appearance characteristic of xanthoma tissue, i. e., it consisted of large round cells, which in ordinary alcohol-fixed preparations showed a reticular structure seemingly composed of small, round or oval, empty cavities. In frozen section of portions fixed in formalin it was found that the cells contained lipoid substances; some were neutral fats, but for the most part they were cholesterol esters, which gave peculiar or characteristic reactions with stains and could be recognized also from the fact that they proved to be dichromic in the polarizing microscope. It is noteworthy that xanthoma tissue was absent in all the tumors in the joint capsules that will be described later.

What is the prognosis in tumors in the sheaths of tendons? In general, it may be considered good. All the tumors except that in case 8 were sharply demarcated and did not recur after extirpation (except in case 3). Tumors of this kind, especially when they are rich in xanthoma tissue, often grow in between the tendons into the periosteum (and even into the bone—case 4). Nevertheless, the prognosis may be said to be good, and minor local operations (without mutilation) are fully justifiable and, doubtless, as a rule, are also sufficient.

The structure also suggests a benign nature. The number of cells, as a rule, is not particularly great; the cells are usually spindle-shaped; the intercellular substance is distinct, moreover often hyaline, indicating a certain slowness in development. The many giant cells point in the same direction, as does also the xanthoma tissue. A tendency to degeneration and cyst formation was observed in several of the tumors, although not pronounced. Cysts may be marked in tumors of this kind or in tumors around joints, as Kirch⁴ has shown.

On the other hand, there can hardly be any reasonable ground for doubt, as raised recently by Arzt,⁵ that these are genuine tumors. Arzt and others assume that the xanthoma really is not a tumor, and that even in tumors containing xanthomatous portions there may be merely a passive deposition of cholesterol-esters in an inflammatory tissue. According to this view, which Fleissig,⁶ among others, has advocated, xanthoma and xanthosarcoma are classed as growths of granulation tissue, but they lack typical signs of inflammation, so that this view can hardly be maintained.

4. Kirch: Beitr. z. path. Anat. u. z. allg. Pathol. **70**:75, 1922.

5. Arzt: Arch. f. Dermat. u. Syph. **126**:907, 1919.

6. Fleissig: Deutsche Ztschr. f. chir. **122**:239, 1913.

Fleissig also assumes that the giant cells in xanthomatous tumors are different from the giant cells in sarcoma. But this assumption does not hold good. In my tendon sheath tumors were all kinds of giant cells and all transitions from ordinary connective tissue cells and endothelial cells to giant cells. A pronounced polymorphism was often seen. Xanthomatous tissue was not infrequently lacking, and yet the tumors from their anatomic structure constituted a unit.

It is likewise impossible to accept the view that the tumors arise through deposition of fat in normal or degenerated tissue. The xanthomatous tissue forms only a small part of the tumors—indeed, it is sometimes entirely absent in tumors that must be classified with tendon sheath tumors—so that the occurrence of xanthoma cells cannot decide whether or not the growth is a real tumor.

Taking all things into consideration, I came to the conclusion that these new formations ought to be regarded as real tumors, and most probably as sarcomas, but of comparatively benign character.

Whether one can reject the idea that the cholesterol must be explained as indicating cholesterolemia in the same manner as in multiple pure xanthoma, is another matter. There is a remarkable concordance in localization, the pure xanthomas also being situated under the skin, around and in the tendons and in the tendon sheaths, often around the heel tendons and around joints, which accordingly seem to be disposed to the formation of both xanthomatous tissue and xanthomatous tumors. The cause of this disposition is not known. Is it a peculiar embryonal development or a peculiar clinical composition of tissue?

Investigation of the blood to determine the cholesterol content in case of tumors of the tendon sheath with xanthomatous tissue has been carried out only to a small extent,⁷ and it is desirable to give more attention to this matter in the future.

II. TUMORS OF THE ARTICULAR CAPSULE AND SYNOVIAL MEMBRANE

These tumors do not form such a well defined group as the tumors of sheaths of tendons, with which, however, they may be connected by transitions. Neither is the point of origin always easy to determine, especially when the tumor is situated, not in the articular capsule itself, but in the subcutaneous tissue around it, for example. The structure is also rather variable. These tumors fall into two groups:

7. In Hoessli's case (*Beitr. z. klin. chir.* **90**:168, 1914) hypercholesterolemia was present. In his patient, a woman, aged 27, symmetric xanthomas occurred in the skin on the elbows and in the tendon sheaths on the fingers—pure xanthoma—so that the case most probably belongs to my group 3, perhaps a transition case.

CIRCUMSCRIBED TUMORS OR INFILTRATIONS OF VARYING STRUCTURES

CASE 1.—In a woman, aged 51, a tumor, the size of a pigeon's egg, developed in the capsule of the knee in the course of two years. It was firm, gray-white, fibrous, not distinctly limited and microscopically a polymorphocell sarcoma, with giant cells in some places, and containing some pigment.

CASE 2.—In a woman, aged 66, a tumor, the size of a walnut, was removed from the capsule of the knee joint. It was firm and hard, with a gray-white, cut surface, microscopically; it proved to be a small cell sarcoma. In the following four years, it did not recur.

CASE 3.—A woman, aged 27, for some years had had a swelling in the recessus superior genus, which microscopically proved to be a flat, firm, fibrous, gray-white tumor, a sarcoma fusocellulare.

CASE 4.—Ostensibly after an injury in a man, aged 26, a peduncular tumor the size of an almond developed in the synovial membrane of the knee joint, a sarcoma fuso-giganto-cellulare, microscopically.

CASE 5.—Ostensibly after an injury to the knee, small tumors developed on the outer side of the capsule in a woman, aged 39. Microscopically this appeared to be a polymorphocell sarcoma.

CASE 6.—The patient had a recurrent polymorphocell sarcoma on the inner side of the knee joint capsule. Death resulted from return of the growth.

CASE 7.—In a woman, aged 71, a large flat sarcoma, fibro-giganto-cellulare, formed in the capsule of the knee joint in the course of five months.

CASE 8.—In a man, aged 22, a sensitive neurofibroma, the size of a bean, developed in the capsule of the knee joint in the course of two years.

CASE 9.—A sailor, aged 58, presented a calcareous fibroma, the size of a goose egg, which had existed for thirty years on the inner side of the knee.

CASE 10.—For fourteen or fifteen years a woman, aged 35, had a slowly growing, small sarcoma, fusocellulare, on the wrist.

The tumors in this group, all of which had their seat in the capsule of the knee joint and the adjacent areas, except that in case 10, form a special group. These tumors resemble the tumors of tendon sheaths, but there are certain differences that justify their classification into a separate group. These tumors, which occur in young and old and which may grow slowly (cases 3, 4 and 10), are, as a rule, rather sharply circumscribed, and are sometimes multiple.

The structure is more purely sarcomatous. Giant cells are not infrequent, and in this the tumors resemble those of the first group; but this is not the case in a pronounced degree. On the other hand, xanthomatous tissue was not found in any of these cases; neither was there much pigmentation. Slow development, with subsequent recurrence, was observed (case 3). Trauma may have been a cause in cases 4 and 5.

An especially malignant tumor is illustrated by case 6, but the point of origin was doubtful (in the skin?). The same applies, moreover, to case 7, in which the tumor possibly developed from the subcu-

taneous tissue. An exceptional position is held by case 8, in which the tumor proved to be a neurofibroma ("neurinoma").

Otherwise, the structure in these cases is fairly uniform, as a rule, the diagnosis of sarcoma distinctly obvious and malignancy pronounced. Undoubtedly the treatment should be in accordance with the degree of malignancy.

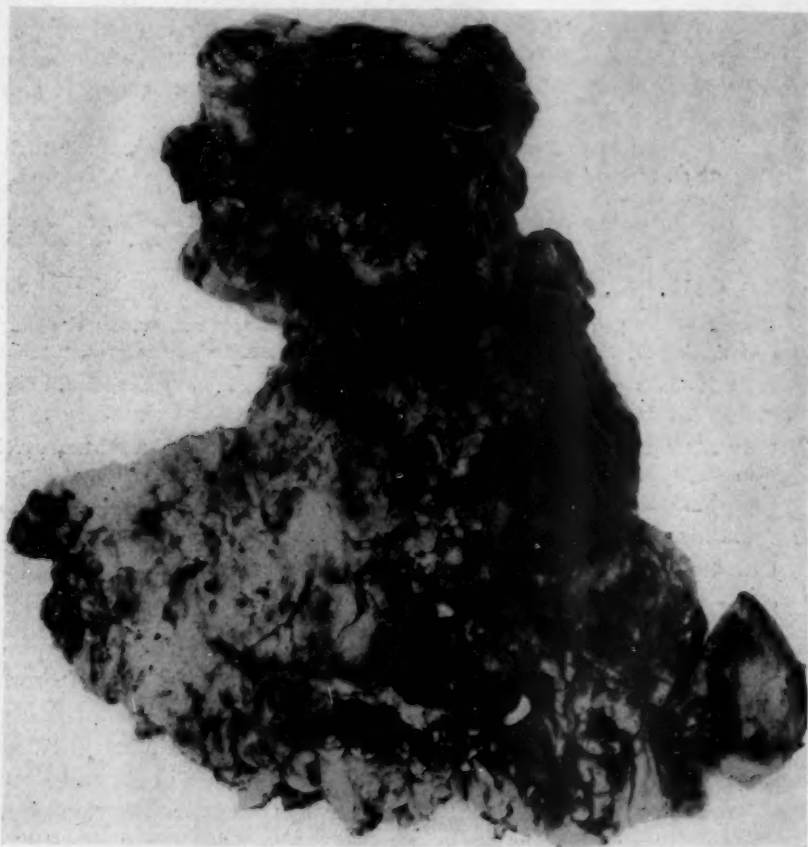


Fig. 5.—Endothelial sarcoma with calcification of capsule of knee joint; showing outgrowths of synovial membrane with incrustations.

DIFFUSE SARCOMA OF THE ARTICULAR CAPSULE, RESEMBLING
TUBERCULOSIS

The nature of chronic diffuse diseases of the joints is not always easy to determine either clinically or anatomically. Many kinds of errors may be made. A tuberculous condition of the joint may take the form of a chronic and relatively benign disease, which may appear, for example, under the picture of arthritis deformans, with little exudate and proliferation of the cartilaginous and osseous portions of the joint;

and the patient may go about for perhaps six, eight or twelve years before an operation is performed which, with subsequent microscopic examination, brings to light the tuberculous nature of the disease.

On the other hand, a lesion of the joint may have the appearance of tuberculosis with involvement of the bone, and may display synovial changes with some resemblance to tubercles, although quite a different condition is really present. I shall describe an example: a rare condition of the joint, namely, a primary sarcoma of unusual appearance in the synovial membrane.

A man, aged 22, for seven or eight weeks noticed a swelling in the joint of the right knee, with pain and some fever. The knee was large, the capsule was thickened in the recessus superior, and there was tenderness over the lateral

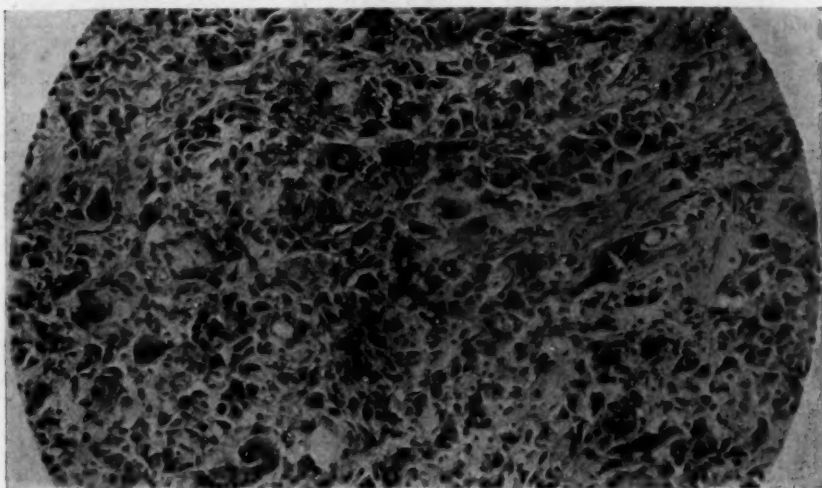


Fig. 6.—Microscopic section of growth shown in figure 5; $\times 160$.

condyle. On roentgen-ray examination, a slight defect was found, as well as periosteal deposits anteriorly on the ends of the femur above the condyles. After the injection of tuberculin (10 mg.), there was a general, but not a focal, reaction. Resection was made under the diagnosis of tuberculosis, and a walnut-sized focus was removed from the lateral condyle of the femur.

The cartilage of the resected ends was sound. In the recessus superior the wall was thickened; on the inner side it was uneven with excrescences, granular and in parts encrusted with lime (fig. 5). Deeper in the wall the capsule was gray-white. Tubercles were not observed. Microscopically, a papillomatous tissue was found in sections through the wall in the recessus superior, in which were seen—corresponding to the granules—amorphous calcareous masses, which extended far up in the papillae. At certain spots, also, small pieces of cartilage were found. The papillae and the tissue into which they merged were, however, exceedingly rich in cells which were assembled in large clusters: Some of the cells, which seemed to be of the nature of connective tissue separated by extremely scanty intercellular substance, were spindle-shaped, some polyhedral,

some large and polymorphonuclear and some as small as lymphocytes. Deep down a few giant cells and roundcell infiltration were also seen. The cells in part resembled endothelium. Indications of tuberculosis were not found.

The tissue of fossa condyloidea and the substance scraped from the cavity in the condylus lateralis had the same structure.

In decalcified preparations from the recessus superior and from the condyles were seen ramifying masses of lime, but no distinct bone or cartilage. Otherwise, the tissue was cellular and tumor-like, with extremely heterogeneous cells, including numerous polyhedral and polymorphonuclear cells (fig. 6). In a blood vessel a number of cells was also seen.

From the structure it was decided that an endothelial sarcoma existed with extensive calcification.

The growth returned. The tissue again had the structure of a polymorphocell sarcoma, with giant cells. The leg was amputated at the thigh. Erosion of the femur was found for some distance above the resection, and large masses of infiltrating brown-yellow tumor tissue, and lime-incrusted places infiltrating the musculature. Microscopically, the cell forms described were found, but they were still more variable and atypical, with spindle-shaped and polyhedral cells, and a number of giant cells, some of them being large. The patient soon died; autopsy was not performed.

Tumors in the articular capsule including the synovial membrane with such diffuse distribution as was seen in this case are rare, and they may be difficult to diagnose. The diffuse distribution and the papillary excrescences may not suggest sarcoma. The slow growth with general swelling of the joint, which may give fluctuation or pseudofluctuation, suggest tuberculosis. Against tuberculosis, on the other hand, speak the relatively good movement, in spite of the swelling of the joint, the absence of crepitation, pain and fever, the absence of atrophy of the peri-articular muscles and the often slow progress of the disease (up to five, six, ten and thirteen years have been reported). Puncture of the joint in most cases yields a clear or sanguinolent fluid, and now and then scattered nodules or distinct separate infiltrations may be felt. The bony parts of the joint are more frequently attacked in tuberculosis than in sarcoma.

Sarcomas in the joints are usually assumed to be comparatively benign, and this, no doubt, is often the fact. But my case, which, however, differed in appearance and structure from the great majority of those previously described, proves that the disease can be malignant and rapid in growth and require radical operation.

In addition, there are comparatively benign diffuse tumors (sarcoma) of the joint, as illustrated by the next case.

In the family history of this case, placed at my disposal by Dr. Sundt, tuberculosis was not mentioned. In the autumn of 1923, a woman, aged 20, noticed that the right knee was gradually swelling. In the summer, she had received a blow on the knee, but she had recovered from the effects. The swelling continued to increase, and in 1924 the knee was immobilized in plaster for six weeks, after a diagnosis of tuberculosis. Pain was never present, and the leg was not weaker

than the other. In May, 1925, the swelling of the knee was most pronounced medially and corresponding to the recessus superior, where the capsule was felt to be thickened. There was relatively good movement.

As the thickening of the capsule persisted and as roentgen-ray examination revealed a considerable narrowing of the joint fissure and atrophy, resection was made in March, 1926. A little sanguinolent fluid was found in the joint. The capsule was red-brown to chocolate-brown (as in chronic synovitis) and thick. The cartilage, especially over the articular surface of the femur, was uneven, at some places thinned, and honeycombed with rough edges. The condylus medialis femoris was partly covered with fibrous tissue, as were parts of the articular surface of the tibia. The synovial membrane was greatly swollen. Nothing suggesting tuberculosis was found.

Microscopically, some of the soft parts were covered with endothelium which was sometimes proliferated. Papillomatous excrescences of a cellular tissue with extremely diversified cells of the nature of connective tissue were present; some were round, some oblong and spindle-shaped and some angular, separated by a scanty intercellular substance. Besides, a number of giant cells of irregular shape with numerous nuclei were scattered in the tissue, sometimes assembled centrally. Quantities of yellow-brown ferriferous pigment were also seen. Finally, small portions of tissue were observed containing fat cells; this tissue had the appearance of xanthomatous tissue. The stroma in places resembled cartilage.

In a decalcified preparation from the articular surface of the femur the same cells were found as in the excrescences; they were endothelial or resembled connective tissue cells, and extended in long lines inward between cartilage and bone, with destruction of the cartilage and erosion of the bone.

From the microscopic picture it must be assumed that a tumor existed, most probably a xanthofibrosarcoma (sive endothelioma), giganto-cellulare pigmentosum. There was no sign of inflammation, nothing resembling, for example, the organization of a blood extravasation or exudation. From its appearance the tumor much resembled those in the sheaths of the tendons (xanthosarcoma), and like these it ought, no doubt, to be regarded as a comparatively benign growth. Nevertheless, its relation to the articular surface showed that it was infiltrating and destructive of cartilage and bone.

III. MULTIPLE SYMMETRICAL XANTHOMA

The tumors of tendon sheaths here described consisted partly of "xanthomatous tissue," i. e., newly formed lipoid tissue of peculiar structure, composed of large cells filled with cholesterol esters. They were local, as a rule solitary, and the xanthomatous tissue formed only a part of the growth. There are also tumors that consist almost exclusively of xanthomatous tissue, pure xanthomas, which usually are multiple and frequently also symmetrical. They occur in the subcutaneous tissue and in the fascia, frequently also in the tendon sheaths, particularly around the knees and elbows, on the hands, in the gluteal region and on and around the tendons at the heel. Sometimes, although seldom, nodosities occur on the eyelids, where xanthomatous tissue (generally called "xanthelasma") is frequent in older people.

This remarkable lesion has attracted much attention, especially among dermatologists. Whether it is a genuine tumor has become more and more doubtful. The fact is that multiple xanthoma seems to constitute a stage in or a symptom of a general condition, a constitutional anomaly in which the blood may be especially rich in lipid substances (cholesterolemia), so that the tumors of the skin may be conceived as local deposits of lipoids circulating in the blood (case 3). These lipid substances may also, as the cases show, be deposited in internal organs, for example, in the mucous membrane of the mouth, the bile ducts in which large infiltrates may even cause stenosis and the walls of the heart and arteries in which they may likewise result in mechanical hindrances.

Another feature points to a constitutional condition, namely, that the tumors occur in certain families, a fact to which Touton has drawn attention (also case 1).

Although it seems reasonable to regard these lesions, this general xanthomatosis, as a constitutional anomaly with local deposits in the skin and inner organs, these deposits often occur in pronounced tumor form and agree also in appearance and partly in localization with xanthomatous tumors in tendon sheaths and about joints. They also may resemble tumors in that a form of recidivation, i. e., a new deposit, may occur after extirpation, while the diffuse infiltration may offer some resemblance to the infiltrating growth of an atypical tumor. Metastasis, on the other hand, never occurs.

The lesion has been long and well known, and a large number of interesting and excellent observations is found in the older English literature. Louis Török,⁸ in 1893, classified older reports in tabular form: xanthomatosis as family disease; juvenile forms, often congenital, thirty cases, and xanthomas in adults, forty cases, often in patients with chronic icterus and diseases of the liver. During recent years, many articles have been published on multiple xanthoma, especially in German and English, notably by Siemens,⁹ Arzt,⁵ Harrison¹⁰ and Parkes Weber.¹¹

REPORTS OF CASES

CASE 1.—A boy, aged 13 years, had always been well, with the exception of an attack of scarlatina when he was 7 years old. In the spring of 1917 swellings began to develop in the tendons of the heel, first on the right and then on the left side, followed by steady growth, without pains or tenderness. A year and a half later, some yellow-white patches appeared in the skin over both knees. He was

8. Török, Louis: *Ann. de dermat. et syph.* **4**:1109, 1893.

9. Siemens: *Arch. f. Dermat. u. Syph.* **136**:159, 1913.

10. Harrison: *Brit. J. Dermat.* **35**:81, 1923.

11. Weber, Parkes: *Brit. J. Dermat.* **36**:335, 1924.

admitted to Stavanger Infirmary (Dr. Ingebrigtsen), April 12, 1919. The boy looked well and was in good condition. Over the distal portion of the tendons of both heels were soft, fluctuating, nonsensitive growths, the size of a hazelnut; in the skin over both knee caps were yellowish, flat, small (half as large as a pea), nonsensitive nodes, in parts confluent.

On April 15, 1919, the lumps at the heels were removed. They consisted of a putty-like substance, which was growing into the tendons. On discharge, a nonsensitive thickening was still present around the tendons of both heels, and infiltrations soon formed again with steady growth and no pain or tenderness. At the same time, small yellow patches appeared in the inner angles of the eyes, grew steadily for some time and then remained stationary. On Aug. 23, 1922, they formed symmetrical, slightly elevated, circumscribed, yellow, soft masses, of irregular outline, 0.5 by 0.2 cm., covered by thin skin. On the left elbow were numerous small yellow masses in the skin (fig. 7). Above the ligament of the triceps tendon was a nonsensitive, soft yellow growth, the size of a hazelnut. On the right elbow was a similar, slightly larger growth, as well as some small masses. There were similar growths over both knee caps. At the heels were nonsensitive, round, soft growths 4 by 4 by 2 cm. The tendons above the tumors

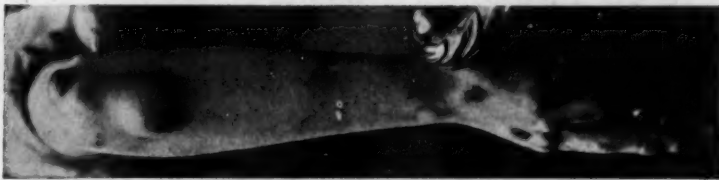


Fig. 7.—Symmetrical fibrolipoma (xanthoma).

were thickened. The ankle joints were normal. Finally, on the last joint of the third finger of the left hand was a hard, round, nonsensitive node the size of a hazelnut, and there were similar and smaller nodes on both hands, corresponding to the metacarpophalangeal joints, one being at the basis of the left fifth metacarpal. On September 4 the growths at the heels, which consisted of ocher-yellow, structureless, fairly firm putty-like masses, without any sharp limits but extending into the achilles tendon, were removed as were also the masses in the skin of both knees and of the right elbow. The masses from the heels were walnut-sized, firmly elastic, striped yellow-white on the outer surface. The masses from the knees and from the right elbow consisted of yellowish confluent nodules up to the size of a hazelnut, covered with unbroken skin.

Microscopically, the picture in sections from all the parts examined was uniform. The masses were composed partly of fibrillary, partly of hyaline, connective tissue, which constituted large parts of the nodes, especially at their periphery. In other parts a more cellular connective tissue was found, which contained numerous rather large, sometimes cubical, sometimes more oblong, cells with abundant protoplasm of varying size and sharp outlines; here, also, were large cells with from six to eight or more nuclei, most often central. The giant cells occurred in distinct groups. And then, as a main constituent, large, swollen, oval cells were found, which resembled connective tissue cells, with a meshlike protoplasm, as in young fat cells "xanthomatous tissue." These cells were assembled in heaps and formed the greater part of the nodes, especially in the central parts (fig. 8). The tissue was traversed by numerous vessels, sometimes

with thickened intima, and here and there surrounded by lymphocytic infiltration. Pigment (hemosiderin) was not found.

Diagnosis: Symmetrical fibrolipomas (xanthomas), in parts more rich in cells (sarcomatous?).

On Sept. 6, 1924, two years after the last operation, Dr. Ingelbrigtsen reported that the growths at the heels and knees had not recurred. In the subcutaneous tissue around the right olecranon was a flat patch, about 2 cm. in diameter, consisting of small, soft growths, above the location of the nodes removed in 1922. About 2 cm. below the scar on the elbow was a soft, flat, oval, lobate growth, covered with normal skin. On the left elbow above the olecranon, as before, were seen small, soft, yellow masses over an area 2 by 2 cm., and the outer edge

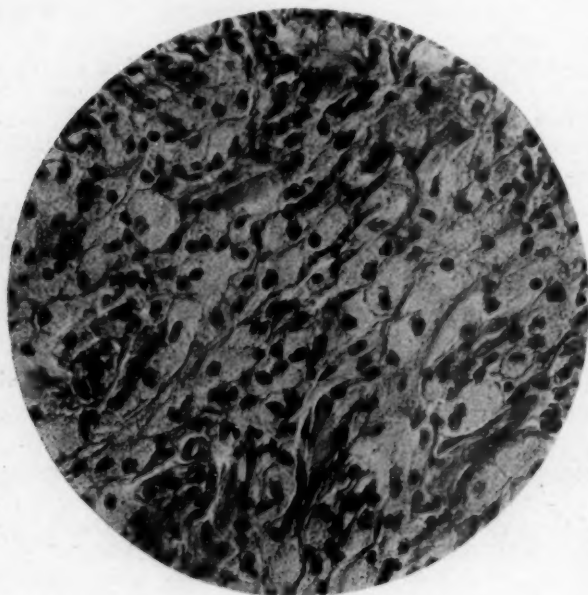


Fig. 8.—Microscopic structure of growth shown in figure 7; $\times 300$.

was a soft, yellow nodule the size of a Spanish nut, with infiltration of the skin. Below the olecranon were small, yellow nodes, symmetrically placed in relation to those on the right side. Round flat nodes were present, also, on the extensor tendons of the hands and on the dorsal side of the terminal phalanx of the third finger on the left hand. The latter was the size of a bean and infiltrated the skin. The boy was otherwise in good health and looked well.

On examination of the boy's father, it was found that he too had small flat, yellow, oblong-shaped nodes in the skin inside the inner canthus. Besides, on the right side at the root of the nose, he had yellow nodes, and the same kind of nodes had been removed from the other side without recurrence. The father said that six of his eight brothers and sisters had similar yellow nodes around the eyes.

CASE 2.—Nothing was known of the family history of a boy, aged 8 years, the only child of a farmer, under the care of Dr. K. Grön. When he was about 1 year old peculiar masses appeared in the skin at the upper end of the cleft of the

buttocks, and on both heels. Fresh eruptions followed. The patient remained generally healthy. On Sept. 11, 1917, the general health was good. The largest nodes (figs. 9 and 10) were on the heels, in the form of egg-sized lobate masses, pale bluish red in the center, but characteristically straw-colored in the periphery. The consistency was soft and elastic. The nodes were later extirpated by Dr. Schilling and were found to be infiltrating diffusely into the soft tissues and the achilles tendons. Around the cleft of the buttocks were a large number of large and small yellow nodes, deposited in the skin in almost symmetrical positions. The largest nodes resembled those on the heels. Further, symmetrical nodes were seen on both elbows, on both knees and on the flexor side of the wrists; nodes were also present on the posterior portion of the helix of the right ear. There were, further, distinctly palpable, and in parts also visible, subcutaneous deposits,



Fig. 9.—Multiple juvenile xanthoma. Fig. 10.—Multiple juvenile xanthoma.

doubtless of the same nature, on both index fingers (symmetrical), and less distinct masses on the backs of the hands and around the wrists. These infiltrations were covered with movable skin and seemed to proceed from the tendons. Along the outer side of both thighs were numerous nodes, which, perhaps, were connected with the periosteum. Finally, deposits were found in the recessus superior of both knee joints, apparently proceeding from the periosteum.

Microscopically, the growths on the heels consisted of lobate masses of large, closely adjacent, sharply circumscribed, round or oval cells, with a small round nucleus, usually central. The protoplasm appeared dissolved, granular and foamy in alcohol preparations. The cells resembled young fat cells, but otherwise showed transitions to connective-tissue-like cells, though they were smaller and more spindle-shaped. These cells often were arranged around long columns, doubtless of lymph or blood vessels, so that cylinders of cells were formed. Inflammation was not present.

Chemical analysis of the blood was not made.

In September, 1924, the boy was reported to be well but looking rather thin and pale.

CASE 3.—Xanthomatosis universalis: In a man, aged 38, the nodules first appeared on the ears, and the linear eruptions and yellow spots developed on various parts of the skin, associated with severe itching. In August, 1920, there were many nodules, mostly small, on the body, on the nape of the neck, symmetrically disposed on the extensor side of the upper part of the arms and on the flexor side of the forearms, on the palms, on some fingers on the nates, on the thighs, on both knees, on the heels and on some of the toes. On the left heel was a mass the size of a walnut. On both elbows were large masses surrounded by smaller, reddish nodes with yellow foci, which were hard and not tender.

Microscopically, the usual picture of xanthoma was seen: closely packed, large cells, most of them resembling connective tissue cells in form, with small round nuclei and fairly clear protoplasm, divided into fields. In the frozen section stained with sudan, granular material in the cells took a reddish stain. Slight dichronism was present. Neutral fat in large quantities was found in the masses by Dr. Fölling, likewise cholesterol esters, as well as traces of pure free cholesterol and of lecithin. The quantity of fat in the blood was greatly increased; a pure lipemia with cholesterol esters was demonstrable.

The patient died suddenly. Autopsy was not performed. Apparently, other cases like his did not exist in his parents, brothers or sisters.

These cases are typical both as to localization (elbows, knees, eyelids, heels, buttocks) and as to form and appearance of the masses: The yellow color is not due to cholesterol-esters, but to yellow coloring matter, belonging to the luteins (especially carotin and xanthophyllin). The first two cases represent xanthoma juvenile multiplex. In case 2 the disease was doubtless congenital; at any rate, lesions developed in the first year. In case 1 the first lesions appeared in the seventh or eighth year, but owing to a decided family disposition to the condition, there does not seem to be any question as to the familial nature of the disease. The characteristic features of the juvenile form, namely, early occurrence on a hereditary basis without any connection with disease of the liver and without involving the eyelids, are well illustrated by these cases. Infiltrations were present in the eyelids, however, in case 1, and perhaps in case 2, and there is no valid reason to believe that a sharp distinction exists between the congenital infantile and juvenile forms on the one hand, and xanthoma in adults on the other. Adult xanthoma has the same localizations as are found in the juvenile forms, but it occurs especially in patients with chronic diseases of the liver.

Case 3, a xanthoma in a man, aged 38, did not, however, have any connection with disease of the liver or of the pancreas or with diabetes mellitus, in which, as is well known, multiple xanthomatous masses may occur in the internal organs. A case of this sort—general xanthomatosis in a soldier with diabetes mellitus—has recently been reported by Lubarsch.¹²

12. Lubarsch: Deutsche med. Wchnschr. 44:484, 1918.

Case 3 is of interest because the patient died suddenly, even though the exact cause is not known; but the fact of sudden death deserves to be noted. In the reports of fatal cases with autopsies (for example, in Török's⁸ tables, in which eight deaths are mentioned), it will be seen, first, that most of the patients died in the third and fourth decades (28, 32, 32, 35, 39 years, etc.), and next, that many of these patients had serious diseases of the internal organs, the liver, arteries, etc. Deposits of xanthomatous masses were found in the mucous membranes, in the alimentary canal, in the circulatory organs, in the bile ducts and in other locations. In the case reported by Karvonen heart disease developed, ending in sudden death at about the age of 40. Arteriosclerotic changes on account of the cholesterolemia may also be considered. Of special interest is the classic case of multiple xanthoma reported by Lebzen and Knauss,¹³ in a girl, aged 11 years, whose sister had the same condition. Beginning at the age of 3 years, nodes appeared in the skin on various typical parts of the body; the growths on the hands finally became larger than a hen's egg. Mitral insufficiency developed, and Leube ascribed it to xanthoma endocardii. The child died suddenly. Post mortem, in addition to the nodes in the skin, large xanthomatous deposits were found in the aorta, with constriction of the isthmus, in the large arteries of the neck and arms, in the coronary arteries and in the mitral valves. It may be recalled that arteriosclerosis has been produced by the feeding of cholesterol (Versé).

The nature of the constitutional anomaly in these cases is still much disputed. In the cases carefully investigated by Arzt⁵ and Siemens⁹ the blood was found to have the normal quantity of cholesterol. In other words, in some cases the tendency to deposition of cholesterol or cholesterol esters is so great that deposition takes place even when the content of these substances in the blood is normal. This shows that the conditions at the places of deposit are of great importance, which also emerges from the definite and characteristic predilection for certain localities, which, presumably, by their chemical nature attract such deposits. But hypercholesterolemia is an important factor, frequently present, and accordingly it ought to be looked for in all cases. It should be borne in mind that as the process may be hereditary, the blood of members of the family who are apparently well should be examined also.

One is reminded of the experiments by Anitschkow,¹⁴ Borst¹⁵ and Yukata Kon¹⁶ on feeding cholesterol or lanolin to rabbits. It will be

13. Lebzen and Knauss: *Virchows Arch. f. path. Anat.* **116**:85, 1889.

14. Anitschkow: *München. med. Wchnschr.* **60**:2555, 1913.

15. Borst: *Ztschr. f. Krebsforsch.* **21**:337, 1924.

16. Kon, Yukata: *Gann, Japan. Ztschr. f. Krebsforsch.*, 1917, no. 3.

recalled that Kon obtained adenomatous and papillomatous formations with cholesterol deposits. Borst noted the development of fibromatous and xanthomatous tissue with papilloma and, in one case, carcinoma.

That there are peculiar cell affinities for the substances in question is indicated by the fact that the deposits take place in definite cell systems. In addition to the connective tissue cells in particular locations, deposits also appear in the cells of the reticulo-endothelial apparatus (in the liver, spleen, bone marrow, lymph glands and other places). So much importance has been attached to this cell system in this connection that it has even been called the "intermediary apparatus in cholesterol metabolism."

But, as stated in the foregoing, if the amount of cholesterol esters in the blood is large, a tendency to local deposits results. This is confirmed by observations that in conditions of hypercholesterolemia in chronic diseases of the kidney, chronic icterus, cholelithiasis, pregnancy and other conditions, local deposits of cholesterol and xanthoma may occur. This is true especially in diabetes mellitus, but in this condition the lesions usually are more acute and are accompanied by pain and itching.

In xanthoma of the eyelids in the old, "xanthelasma," hypercholesterolemia has also been observed.

If one looks on multiple symmetrical xanthomas as resulting from a constitutional condition, they cannot be considered tumors in the true sense of the term, however much they may resemble tumors in external appearance. Treatment should be adapted to this fundamental conception of their nature. The infiltrations in and under the skin should be removed only for mechanical or cosmetic reasons. Whether it is possible to counteract the tendency to deposits by diet or drugs is an unsolved problem.

IV. CLASSIFICATION OF THE "XANTHOMATOUS" CONDITIONS AND PSEUDOXANTHOMA

The classification of the pathologic conditions under which one encounters "xanthomatous" tissue is still a matter of dispute, as is likewise the nomenclature. The main lines of the classification proposed by Aschoff and his pupil Kammer¹⁷ are as follows:

1. Genuine "xanthomas" with subdivisions into: (a) unmixed tumor-like formations, consisting only of xanthomatous tissue and (b) mixed tumors, i. e., fibroma, sarcoma, etc., with xanthomatous tissue.

2. Xanthelasmatic conditions, which occur in diseases of metabolism; for example, in diabetes mellitus, renal atrophy and diseases of the liver, especially

17. Kammer: Ein Fall von Riesenzellenxanthosarkom und über das Xanthom im Allgemeinen, Dissertation, 1909.

when the tissue has a tendency to degeneration. The name "xanthelasmatic" is, however, open to question, since the word is used to designate the xanthomatous tissue that often occurs in the eyelids in old people.

3. Pseudoxanthomas, i. e., deposits of xanthomatous tissue in local inflammatory foci, especially where adipose tissue is undergoing absorption. Such tissue is found, for example, in the gallbladder and in dermoid cysts.

This classification is in many respects unsatisfactory. Thus, the growths under 1 *a* are classed as genuine tumors. It would seem more reasonable, in accord with Siemens and with the principle I have followed, to designate two groups as follows:

1. The development of xanthomatous tissue in disturbances of metabolism, often combined with hypercholesterolemia, with usually multiple, frequently symmetrical xanthomatous growths as the sole form of lesion—a disease *sui generis* or appearing as a symptom of diabetes, hepatic diseases or other conditions. Senile xanthelasma doubtless belongs here.

2. The development of xanthomatous tissue without general disturbances either (*a*) in genuine tumors or (*b*) in "pseudo-xanthomatous" formations, i. e., cholesterol deposits in inflammatory infiltrations or degenerated tissue.

"Pseudoxanthoma" is well known. It occurs especially in purulent granulation tissue, for example, near the kidney, from extension of a pyelonephritic process, about the bile ducts, in various tumors.

In genuine tumors xanthomatous tissue sometimes is an essential part of the neoplasm, and in such cases may give to the tumor a highly characteristic yellow color.

SUMMARY

"Sarcomas" of the tendon sheaths (with giant cells, pigment and xanthomatous tissue) are true tumors, but benign, as they do not recur after thorough removal, and do not form metastases.

Circumscribed tumors of the articular capsule or synovial membrane are generally malignant sarcomas. There exists, also, a diffuse sarcoma of the articular capsule, which may resemble tuberculosis; it often acts as a benign growth, and, rarely, as a highly malignant growth.

The multiple, often symmetrical, pure "xanthoma" with characteristic localizations around the knees and elbows, in the gluteal region, on the hands and feet along the tendon sheaths and on the eyelids are not genuine tumors, but tumor-like deposits resulting from a constitutional disease; as a rule, they are accompanied by hypercholesterolemia. In such cases sudden death frequently occurs, caused, perhaps, by internal localizations—for example, in the heart.

SPONTANEOUS RECESSION OF MULTIPLE PIGMENTED MOLES *

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NEW YORK

The partial or complete recession of benign or malignant tumors is of interest, for it is evident that if on rare occasions forces within the human organism can bring about spontaneous recession of a tumor, the human intellect will some day master the mechanism of the process and develop a medical rather than a surgical cure for the condition. The recording of individual observations is, therefore, of importance.

REPORT OF CASE

A married nullipara, aged 29, a school teacher, noted the spontaneous recession of a number of pigmented moles. She was of the type which usually suggests pituitary disturbance. She had a beginning girdle obesity, large hands and feet, and showed a late sexual maturity. Her skin was of an olive tint, although she was not of Latin derivation. Scattered over the face, extremities and trunk were a number of pigmented moles. The present observation concerns four moles on the back. These were inky black, with wartlike surfaces raised from 1 to 1.5 mm. above the skin and they varied in size up to 2 cm. in diameter. They had the appearance of lesions which often suddenly show the characteristics of malignant melanoma.

The past history was negative; the patient had never been confined to bed because of illness. One year before, a hematoma of the buttock developed as the result of a fall; this was followed by the development of a cyst, due to non-absorption of the blood. The cyst was removed under local anesthesia (procaine hydrochloride) and the recovery was uneventful. Shortly after the operation, the patient noted a faint white line developing about three of the moles. At the same time, the moles, previously of soft consistency, became hard. No general reaction on the part of the body was noted.

Seven months after the onset of the process, one mole had completely receded, the former site being indicated by a circular patch of leukoderma. Another mole remained unchanged. Two other moles were surrounded by irregular circular zones of leukoderma, inside of which was skin showing congestion. The congested area surrounded what was left of the original mole, the mole itself being dry, hard and brownish red instead of black.

The histologic changes cannot be described, since biopsy was refused. The observed changes cannot be due to interference with the blood supply because of the anatomic distribution of the moles. A general reaction, with antibody formation, might explain the changes, except for the fact that not all the moles, even in the general region, have receded. The photographs illustrate the appearances.

* From the Achelis Laboratory, Lenox Hill Hospital.

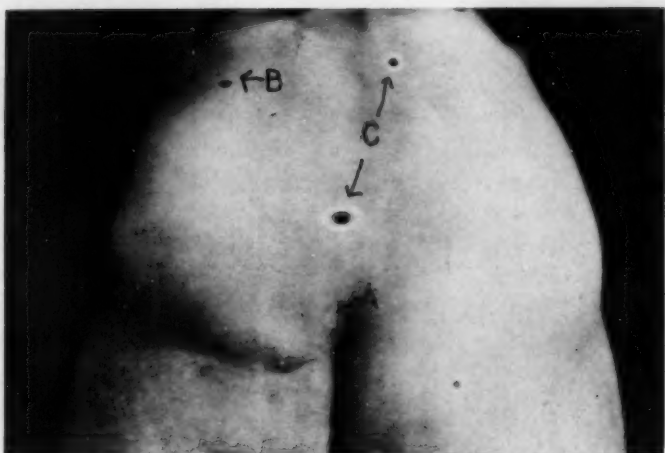


Fig. 1.—*A*, completely receded mole; *B*, unchanged mole; *C*, two moles in process of recession.

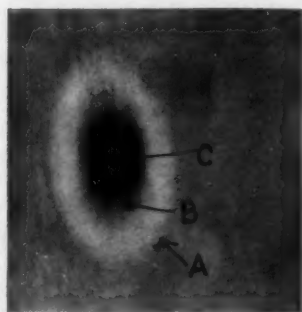


Fig. 2.—*A*, area of leukoderma; *B*, area of congestion; *C*, remaining portion of mole.

THE EFFECT OF HIGH PROTEIN DIET ON THE KIDNEYS

AN EXPERIMENTAL STUDY *

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AND

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There is general agreement concerning the observations of a physiologic enlargement of the kidneys of animals maintained on a high protein dietary, but contradictory results are reported concerning the part played by such rations in the production of pathologic renal lesions.

The character of the physiologic enlargement has been the subject of prolonged dispute. The literature on this question has been summarized by Arataki¹ (1926), who from his own studies on rats found that there is no increase in the number of glomerular-unit systems but that there is an enlargement in the size of both the glomeruli and the tubules—a hypertrophy—together with an actual cellular increase of the interstitial tissue—a hyperplasia. He believed, in addition, that there is a hyperplasia of the constituent cells of the glomeruli and tubules. Furthermore, he observed that the enlargement is incomplete after eighty days, and stated that in some instances it may approximate 100 per cent.

In a study of the compensatory enlargement of the opposite kidney after ligation of one ureter in white rats, Hinman² (1923) has stated that the histologic changes of compensatory renal hypertrophy may be divided into three stages: first, initial congestion; second, active mitosis and growth, and third, the final equilibrium of hypertrophy. He mentioned further that the increase in the size of the intact kidney is complete after an average of from twenty to thirty days; the average total increase is 20 per cent of the normal, and doubling of the renal tissue is never observed. The question of diet is not discussed in either of the papers mentioned.

In intact animals, Osborne, Mendel, Park and Winternitz³ (1927) reported enlargement of the kidneys of white rats maintained on

* From the Department of Surgery and the Laboratory of Physiological Chemistry, Yale University School of Medicine.

* Read before the Section on Pathology and Physiology at the Seventy-Eighth Annual Session of the American Medical Association, Washington, D. C., May 19, 1927.

1. Arataki, M.: *Am. J. Anat.* **36**:437, 1926; **36**:399, 1926.

2. Hinman, F.: *J. Urol.* **9**:289, 1923.

3. Osborne, T. B.; Mendel, L. B.; Park, E. A., and Winternitz, M. C.: *J. Biol. Chem.* **71**:317, 1927.

diets containing excessive amounts of protein. Miller ⁴ (1925) reported similar observations in the remaining kidney of rats after a unilateral nephrectomy.

The production of structural renal damage by feeding excessive amounts of protein has been extensively studied. In experiments on rabbits, Newburgh ⁵ (1919) and Newburgh and Clarkson ⁶ (1923) described evidence of acute and chronic renal disease after relatively prolonged feeding with excessive amounts of protein (egg white, casein, soy beans and lean beef). Evans and Risley (1925) described definite tubular and glomerular lesions in white rats maintained for from six to fifteen months on diets containing high concentrations of protein. In the experiments mentioned the diets were not only extreme but were also inadequate in salts and vitamins.

Polvogt, McCollum and Simmonds ⁷ (1923) made similar studies on white rats, with diets adequate for maintenance and growth and containing between 31 and 41 per cent protein. The time of feeding varied from a minimum of 129 to a maximum of 485 days. Congestion, degeneration of the tubular epithelium, casts and cellular detritus in the lumina of the tubules, hyaline material within the capsular space and adhesions between the glomerular tuft and Bowman's capsule were described in the kidneys of these animals.

Osborne, Mendel, Park and Winternitz ⁸ observed tubular and glomerular lesions in the kidneys of eighteen white rats that had been fed high protein diets for long periods. These authors state that the lesions were focal in nature and were exceedingly slight in the entire group with the exception of seven animals, five of which were on a 40 per cent casein diet for 400 days or more. Exactly similar lesions were observed in five of the control animals maintained on Sherman's stock diet for more than 500 days. The series also included eighteen rats on high protein diets (from 60 to 95 per cent) for periods varying from 200 to 360 days in which no renal lesions were observed. The average age of the animals on the high protein diet which showed lesions was 348 days, while those showing the lesions described as "severe" were more than 400 days old.

4. Miller, A. J.: *J. Exper. Med.* **42**:897, 1925.

5. Newburgh, L. H.: Production of Bright's Disease by Feeding High Protein Diets, *Arch. Int. Med.* **24**:359 (Oct.) 1919.

6. Newburgh, L. H., and Clarkson, S.: Renal Injury Produced in Rabbits by Diets Containing Meats, *Arch. Int. Med.* **32**:850 (Dec.) 1923.

7. Polvogt, L. M.; McCollum, E. V., and Simmonds, N.: *Bull. Johns Hopkins Hosp.* **34**:168, 1923.

8. Osborne, T. B.; Mendel, L. B.; Park, E. A., and Darrow, D.: *Proc. Soc. Exper. Biol. & Med.* **20**:452, 1923.

On the other hand, numerous investigators—Osborne, Mendel, Park and Darrow⁸ (1923), Osborne, Mendel, Park and Winternitz,⁹ in a preliminary report (1925), Drummond, Crowden and Hill¹⁰ (1922), Reader and Drummond¹¹ (1925), Miller,⁴ Jackson and Riggs¹² (1926), Anderson¹³ (1926), Addis, Mac Kay and Mac Kay¹⁴ (1926) and Kennedy¹⁵ (1926)—reported that pathologic structural changes were not observed in the kidneys of intact animals (white rats, rabbits and cats) maintained on high protein diets for relatively long periods. There is thus confusion in the literature on a point which is of academic interest and also of clinical importance.

Our purpose in this communication is to report experimental studies on the effect of the level of dietary protein on the remaining kidney of adult white rats following a unilateral nephrectomy.

TABLE 1.—Composition of Experimental Diets

	"Standard" Food		"High Protein" Food	
	Part of Diet Per Cent	Part of Total Calories Per Cent	Part of Diet Per Cent	Part of Total Calories Per Cent
Protein (casein)*.....	18	14	85	76
Carbohydrate (raw cornstarch).....	51	39
Fat lard	22	..	7	..
cod liver oil.....	5	47	4	24
Salt Mixture (Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. 37:557, 1919).....	4	4	4	..
700 mg. dried yeast given daily with each of the diets				

* A commercial product containing 13 per cent nitrogen.

EXPERIMENTS

Methods.—The plan of the experiment was to remove the right kidney from adult rats, to place the animal immediately on the ration to be used, and after a definite interval of time to remove the remaining kidney for study. This procedure was carried out with the "standard" food, a diet containing the minimal amount of protein for optimal growth and maintenance and likewise with the "high protein" diet, which was unusual in that it contained a high concentration of protein (table 1). Adult white rats were used to eliminate the factor of

9. Osborne, T. B.; Mendel, L. B.; Park, E. A., and Winternitz, M. C.: *Am. J. Physiol.* **72**:222, 1925.

10. Drummond, J. C.; Crowden, G. P., and Hill, E. L. G.: *J. Physiol.* **56**:413, 1922.

11. Reader, V. B., and Drummond, J. C.: *J. Physiol.* **59**:472, 1925.

12. Jackson, H., Jr., and Riggs, M. D.: *J. Biol. Chem.* **67**:101, 1926.

13. Anderson, H.: *Experimental Renal Insufficiency*, *Arch. Int. Med.* **37**:313 (March) 1926.

14. Addis, T.; MacKay, L. L., and MacKay, E. M.: *J. Biol. Chem.* **71**:139, 1926.

15. Kennedy, W. P.: *Quart. J. Exper. Physiol.* **16**:281, 1926.

growth as far as possible. In all, the data on considerably more than 300 rats are available. The kidneys were studied in the following manner: After the kidneys were carefully weighed, while they were free of fat and structures of the hilum, many of the specimens were prepared for histologic study, while the others were used for determinations of the total solids. The animals were, approximately, from 275 to 350 days old at the completion of the experimental period.

RESULTS

Rate of Enlargement of Kidneys.—The data of the experiments on rats fed the standard diet are summarized in figure 1.¹⁶ There is a rapid increase in the compensatory enlargement (24 per cent) of the

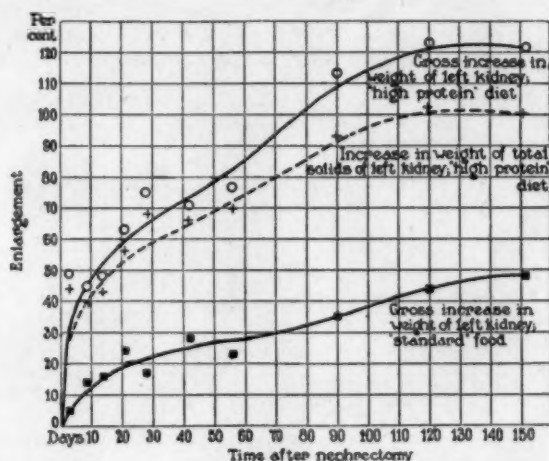


Fig. 1.—The rate of enlargement of the remaining kidney after unilateral nephrectomy. The circles indicate the actual values; the plus signs, total solids and the black squares, "standard" food.

remaining kidney within the first three weeks. From the twenty-first to the one hundred and twentieth day, there is a steady increase at a slower rate, but there is no significant difference between the value at 120 days (44 per cent) and at 150 days (48 per cent).

A similar series on the "high protein" ration (85 per cent casein) shows an extremely rapid rise to 49 per cent in three days. From the third to the one hundred and twentieth day there is a steady rise at a slower rate, and here again there is no significant difference between the value at 120 days (123 per cent) and at 150 days (121 per cent). The figures on the "standard" and the "high protein" diets both suggest that the limit of enlargement is reached after about 120 days.

16. The method of calculating the enlargement is given by Smith, A. H., and Moise, T. S.: *J. Exper. Med.* **45**:263, 1927.

The enlargement illustrated by the foregoing data apparently occurs in response to the protein content of the diet. In an attempt to determine the ratio between the concentration of protein in the diet and the degree of compensatory renal enlargement, a series of experiments was carried out in which the rats were maintained for a constant interval (twenty-one days) after a right nephrectomy on diets containing variable amounts of protein. The data in figure 2 show the degree of enlargement plotted against the percentage of casein in the diet. The curve indicates that there is practically a direct proportion between the degree of compensatory enlargement and the concentration of the dietary protein. The enlargement of the remaining kidney varies from 24 per cent with the standard diet to 77 per cent with a ration containing 90 per cent casein.

The results suggest the question of the relative importance of an actual increase in renal tissue and of an accumulation of fluid in the

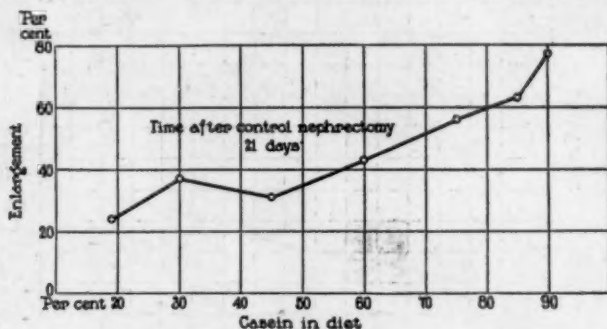


Fig. 2.—The relation of renal enlargement after unilateral nephrectomy to the concentration of dietary protein.

kidneys as factors in the gross renal enlargement. Data on this point have been obtained by determinations on the total solids of normal kidneys and of the enlarged kidneys caused by the high protein diet. The average percentage of total solids in the enlarged kidneys was used to compute the net enlargement of the tissues, and the results are given in the form of a curve (fig. 1). The values in the three to fourteen day group for gross increase in kidney weight and the net enlargement of the tissues vary within narrow limits, but in the longer time interval there is a significant difference between the two figures, which steadily increases to a maximum difference of 21 per cent for the 150 day period.¹⁷

Structural Renal Changes.—Although there is no significant anatomic evidence of renal injury in the animals on the "standard" diet, the kidneys of the rats on the "high protein" diet show some interesting

17. Smith, A. H., and Moise, T. S.: J. Exper. Med. 45:263, 1927.

structural changes. In the early and middle periods, excluding the phenomenon of gross enlargement, the observed changes are relatively inconsequential. However, in the late periods, namely, after 90, 120 and 150 days following nephrectomy, the kidneys of the animals on the high protein ration show significant glomerular and tubular changes.

These changes represent actual lesions of the kidney and were observed in all animals maintained on the high protein ration for ninety days or more after the nephrectomy. The lesions were not merely isolated focal changes but were conspicuous and relatively widespread,

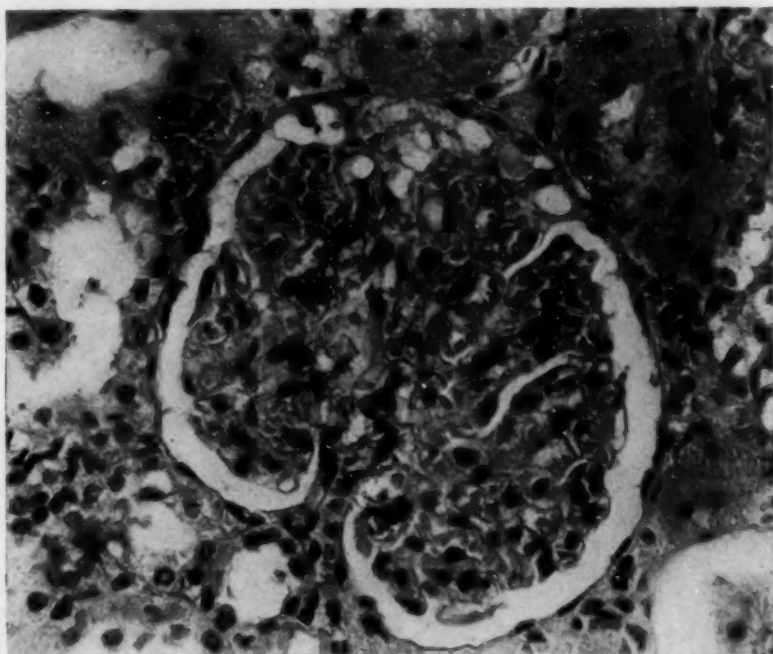


Fig. 3.—High protein diet for 150 days following a right nephrectomy. There is a fresh adhesion between the glomerular tuft and Bowman's capsule. Strands of fibrin are seen connecting the capsule and the tuft in the upper portion of the figure; $\times 400$.

becoming progressively more marked in the 90, 120 and 150 day periods. The structures included in an injured area are frequently radial in form, suggesting the involvement of individual glomerular unit systems.

The changes in the glomeruli consist of serum in the capsular spaces, proliferation of the epithelium of Bowman's capsule with and without adhesions between the tuft and capsule, fibrous thickening of Bowman's capsule, partial fibrosis of the glomerular tuft and in many instances infiltration of round cells in and around these areas (figs. 3, 4 and 5).

In the same periods, 90, 120 and 150 days, the tubules show a conspicuous desquamation of the lining epithelium with fairly well preserved epithelial cells and amorphous material within the lumina. There is a slight general tubular enlargement with a somewhat diffuse patchy distribution of areas of marked dilatation. In these dilated tubules, the epithelium may form a single relatively flat layer or it may appear in many layers as projections into the tubules which in some

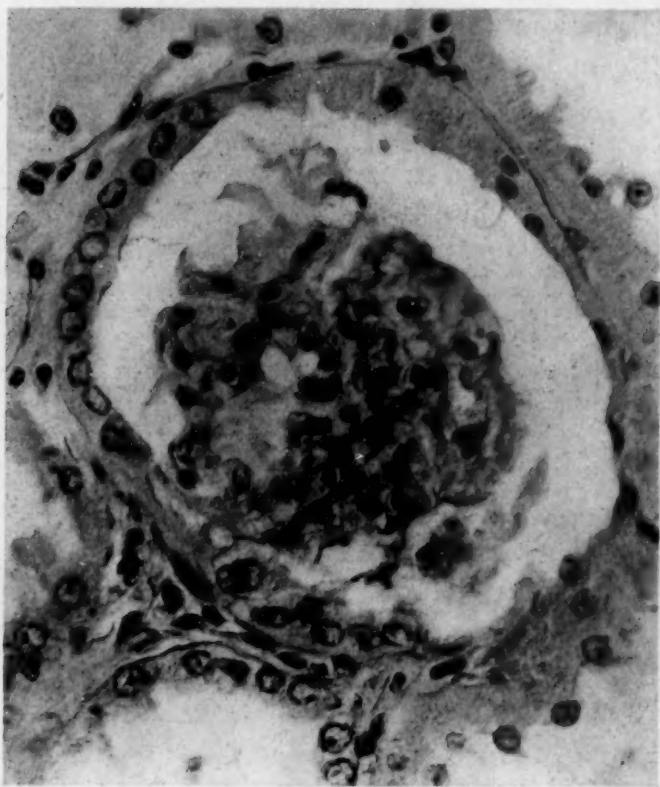


Fig. 4.—High protein diet for 150 days following a right nephrectomy. There is a proliferation of the lining epithelium of Bowman's capsule. The mitotic figure in the lower portion of the illustration is indicative of the activity of the process; $\times 500$.

instances practically fill the lumina. In many such tubules, the lining epithelium consists of recently formed cells containing mitotic figures which are indicative of active epithelial proliferation. There are many focal groups of dilated tubules with flattened epithelial lining cells that do not show any evidence of cellular activity. In some of the dilated tubules, hyaline casts are seen. There are other areas showing an increase in the interstitial tissue with a variable amount of round cell

infiltration. Red blood cells do not appear in the tubules or in the capsular spaces.

These changes are, chiefly, late manifestations of the injury or irritation to which the kidney has been subjected. It seems probable that the irritation produces slight changes in the early periods but that the methods of study only demonstrate the later aspects of the process.

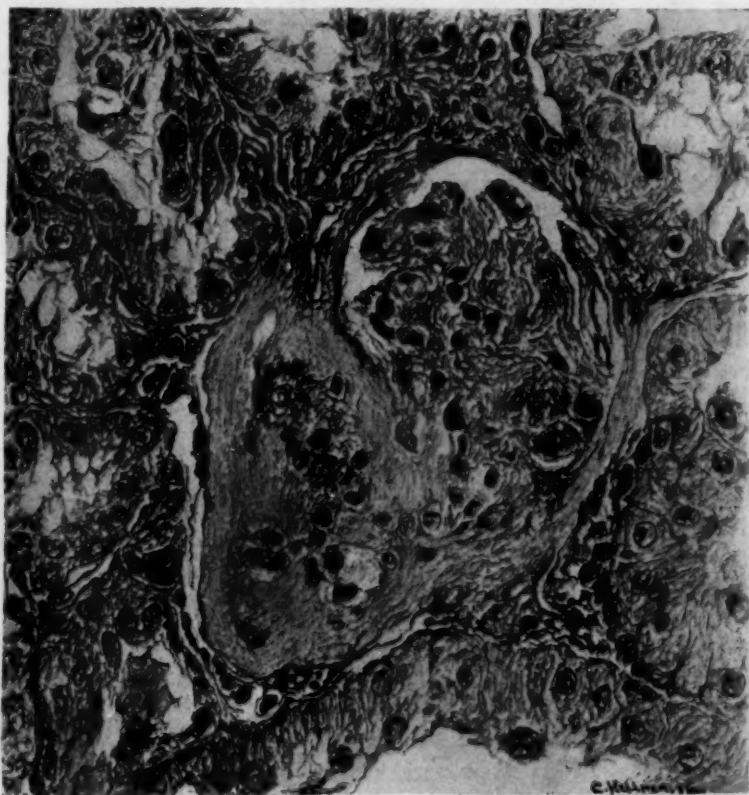


Fig. 5.—High protein diet for 150 days following a right nephrectomy. There is a large fibrous adhesion between the tuft and capsule with fibrosis of approximately one half of the tuft; $\times 400$.

In some instances, the tuft and capsule are in actual apposition or the space is bridged by strands of fibrin. These observations suggest fresh adhesions and are possible precursors of the fibrous adhesions observed in the late periods. Such apparently fresh adhesions were observed in a single section twenty-one days after nephrectomy, and in several instances in the animals maintained on the high protein diets, 150 days after nephrectomy.

In addition to these actual lesions of the kidney, other changes of a physiologic nature occur. In the normal rat's kidney, a few glomeruli are found in which the tubular epithelium extends into and partially lines the glomerular sac. This condition is observed more frequently in the animals on a high protein diet and may involve fully one half of the circumference of Bowman's capsule. It seems probable that this is a compensatory phenomenon whereby the tubular epithelium, in response to a functional demand partially replaces the normal lining of Bowman's capsule. In the early periods, in spite of the extraordinarily rapid renal enlargement, there is no histologic evidence of cellular proliferation in the kidneys of the animals on the high protein regimen. In the late periods, the physiologic enlargement is apparent in the increase in the size of the individual constituent parts of the kidney. Although actual measurements were not made, the tubules were considerably dilated in all rats subsisting on the high protein diets for ninety

TABLE 2.—*Correlation of the Protein Excretion in Urine with Diet **

Interval After Nephrectomy in Days	1 25-53	2 60-72	3 88-110	4 122-143
Number Rats
Standard diet.....	6	4	9	11
High protein diet.....	7	4	10	13
Number Determinations
Standard diet.....	31	16	43	63
High protein diet.....	30	17	67	53
Average value for 24 hours. Urine protein-mg.
Standard diet.....	33	35	28	18
High protein diet.....	31	50	63	63

* The average value of protein in twenty-four hour urine in six intact rats on standard ration was 32 mg.

days or more after unilateral nephrectomy. In some animals, this dilatation was striking. The tubular epithelial cells and the glomerular tufts and the sacs also appeared to be larger in the animals on the high protein diet after ninety days. In the animals on the high protein diet for shorter periods, the enlargement of the constituent parts of the organ was less evident but could probably be demonstrated by actual measurements. There was no evidence of infection in the kidneys of the experimental animals.

The excretion of urinary albumin was studied as a supplement to the histologic study referred to in the foregoing paragraphs. It is known that intact rats, on a mixed adequate diet, constantly show small quantities of protein in the urine (Nelson and McCay¹⁸ and Jackson and Riggs¹²). A comparative study of the albuminuria in the rats fed the high protein diet and those fed the control food was made. The urine was examined for casts at the same time that the determinations of protein were made. The rats used were males, aged 120 days at the time of the

18. Nelson, V. E., and McCay, C. M.: Proc. Iowa Acad. Sc. **31**:286, 1924.

initial nephrectomy, and the determinations were made at short intervals from 25 to 143 days after the operation.

The data are summarized in table 2. In order to obtain a large enough number of observations to permit a statistical treatment, the results were grouped into four periods depending on the time interval after the control nephrectomy; although this grouping is arbitrary, it is obvious that at any period chosen after sixty days, the animals on the food rich in protein excrete significantly larger quantities of albumin than the rats on the standard ration.

There is a tendency for the values in the latter group to decrease with time after nephrectomy, while in the rats in the former group the albumin values increase to a level reached at about ninety days. As an additional control, six intact rats were fed the standard food and the excretion of albumin was measured. The value for the twenty-four hours' elimination, namely, 32 mg., is practically the same as those of the animals mentioned in the description of period 1. In periods 3 and 4, including those intervals in which the structural damage was observed, the increase in the albuminuria was accompanied by the presence of casts in many instances.

COMMENT

The necessity for adequate control in the differentiation of spontaneous renal disease and changes attributed to any experimental procedure is obvious and, accordingly, it is important to recognize the occurrence of spontaneous renal lesions in rats. In a study of wild rats, Ophüls and McCoy¹⁹ (1912) noted the common occurrence of a characteristic type of nephritis. Reader and Drummond¹¹ observed that focal renal lesions are not uncommon in white rats. In the present investigation, the occurrence of such changes in normal animals has been recognized.

There is little doubt that the structural changes observed in the animals on the high protein diet are a result of the experimental procedure and are not purely a part of the spontaneous renal changes that occur in white rats. In the present experiments actual renal lesions, including a proliferation of the tubular and capsular epithelium, adhesions between and a partial fibrosis of the glomerular tuft and capsule, were observed in animals maintained for ninety days or more after a unilateral nephrectomy on a diet containing 85 per cent casein. The kidneys of the animals on the high protein ration also showed marked tubular dilatation, including a diffuse change with evidence of active regeneration of the epithelium. There are, in addition, other areas apparently atrophic in nature, showing groups of dilated tubules with flattening or absence of the epithelium and without evidence of regen-

19. Ophüls, W., and McCoy, G. W.: *J. Med. Research* **26**:249, 1912.

eration. The latter groups of dilated tubules may be secondary to an injured glomerulus.

The lesions observed in animals fed the food high in protein are widespread in distribution in contrast to the relatively inconspicuous focal lesions observed in the control animals. These focal changes are not infrequently observed in normal adult white rats more than a year old; accordingly, in the interpretation of our data, no significance has been attached to isolated renal lesions, among which are included areas of tubular dilatation with and without round cell infiltration and, rarely, a glomerulus showing thickening of the capsule or an adhesion between this structure and the tuft.

These changes are apparently phenomena of senescence and were observed regardless of the composition of the diet, becoming progressively more common with age. These lesions were not found in the kidneys of control animals maintained on a normal dietary regimen for 120 and 271 days, respectively. Observations were made on the kidneys of rats maintained on Sherman's stock diet, whole wheat and milk, for periods between 350 and 565 days. At 350 days, these focal lesions were inconspicuous or were entirely absent; they became progressively more common and after 500 days, they were present in a high percentage of animals. It is interesting to note in this connection that Arataki has observed a normal decrease in the total number of glomeruli with advancing age, and it is possible that the spontaneous focal lesions are secondary to the normal process of glomerular involution.

In the experimental animals maintained on the standard ration, such changes were practically never seen, while in the animals on the high protein regimen the focal lesions were larger and were more frequently observed than in normal rats.

In searching for an explanation of the disagreement between the results reported by earlier investigators, we¹⁷ have suggested that young animals may have greater powers of adaptation and accordingly may be less susceptible to the injurious influence of a diet containing excessive amounts of protein. This suggestion is based on the studies of Arataki,¹ who has observed the continued formation of glomeruli during the first hundred days of life; on the fact that in a large proportion of the observations published that did not report any pathologic renal lesions the experiments were initiated on young rats, and finally on the results of a small number of preliminary experiments in which a greater resistance to the injurious effects of high protein diets was observed when a unilateral nephrectomy was performed shortly after weaning rather than at a later period of life.

Although the exact mechanism whereby structural lesions develop in animals ingesting excessive amounts of protein is not clear, two probable factors are suggested; either the changes are associated with

the increased burden per se on the kidney, or, what is more probable, they result from the elimination of some injurious product of protein metabolism.

The proliferative character of the epithelial changes suggests the persistent action of a mild irritant which does not produce extensive necrosis but which, by continual or frequently repeated slight injuries, finally results in the lesions described. In the present studies, the high acidity of the urine, the phosphates, the urea and the amino acids must be considered as possible factors. Addis, Mac Kay and Mac Kay¹⁴ have shown that anatomic lesions are not produced in a normal white rat with two kidneys by feeding diets containing an excessive acid or phosphate content. On the other hand, Newburgh et al. (1925)²⁰ have described renal lesions after the intravenous administration of certain amino acids (lysin, histidin, tyrosin, tryptophan and cystin). Furthermore, Hinman,² Osborne, Mendel, Park and Winternitz³ and Addis, Mac Kay and Mac Kay¹⁴ were not able to demonstrate consistent renal enlargement when quantities of urea equivalent to the protein in the diet were given. These observations suggest that increased work is not the only important factor, but they do not eliminate the possibility that the persistent effect of unusually large quantities of urea over long periods may result in structural damage to the kidney. However, it should be emphasized that the physiologic strain on the functioning renal tissues has been magnified in our experiments by the removal of one kidney. Further investigation is necessary to determine the specific factor involved in the production of the lesions under the experimental conditions outlined in the present study.

SUMMARY

The rate of compensatory enlargement and the structural changes in the remaining kidney after a unilateral nephrectomy have been studied in adult rats maintained on diets containing different concentrations of protein.

A curve showing the enlargement of the kidney on the "standard" food (18 per cent casein) indicates a rapid initial increase, with a subsequent slower rise for 120 days. There is no significant difference between the value at 120 days (44 per cent) and that at 150 days (48 per cent).

In animals maintained on diets containing increasing concentrations of protein for a constant interval (twenty-one days) after a nephrectomy, the increase in the degree of renal enlargement is directly proportional to the protein content of the food. The values vary from 24

20. Newburgh, L. H.; Marsh, P. S.; Clarkson, S., and Curtis, A. C.: Dietetic Factor in Etiology of Chronic Nephritis, *J. A. M. A.* **85**:1703 (Nov. 28) 1925.

per cent with the 18 per cent casein diet to 77 per cent with the 90 per cent casein ration.

With the "high protein" food (85 per cent casein), the enlargement varies from 49 per cent at 3 days to 121 per cent at 150 days. There is no significant difference between the value at 120 days (123 per cent) and that at 150 days (121 per cent). Determinations of total solids in the kidneys of animals in this group show that the enlargement involves mainly an actual increase in tissue.

In the kidneys of the animals on the high protein ration, actual glomerular and tubular lesions were observed in the 90, 120 and 150 day periods after nephrectomy. Significant renal lesions were not observed in the animals maintained on the standard diet for corresponding time intervals.

The animals on the high protein ration excreted significantly larger quantities of protein in the urine and showed a higher incidence of casts in periods roughly corresponding to those in which anatomic lesions were observed than did the rats on the standard diet.

It is suggested that the age factor is of importance in that young animals may have greater powers of adaptation in withstanding the injurious effect of high protein rations.

The immediate clinical application of these results should be made with great caution in view of the facts that the experimental animals had only one kidney and that the high protein ration, although adequate, was extreme.

ACUTE SUPPURATIVE AORTITIS SUPERIMPOSED ON SYPHILITIC AORTITIS

REPORT OF A CASE *

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AND

GEORGE W. COOPER, M.D.

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Primary acute aortitis is a rare disease and is rarely mentioned in the literature. The combination of an acute purulent aortitis with syphilitic aortitis seems still rarer, and, aside from Rappaport's¹ recent article, we could not find a similar case in the literature. Therefore, the following case, which is in some respect similar to that of Rappaport, may be of interest.

REPORT OF CASE

Clinical Data.—A negro man, aged 50, entered the hospital with the complaint of pain in the chest and shortness of breath. The history did not reveal any signs of a previous acute infection. Syphilis was denied. Clinical examination showed an enlarged heart and a systolic murmur which could be best heard in the region of the aorta. The Wassermann reaction was negative. The blood culture showed *Diplococcus lanceolatus*. The clinical impression was an acute vegetative endocarditis of the aortic valve. Death was supposedly due to an acute infection.

Autopsy Observations.—The body was well developed and well nourished. A marked ecchymosis of the right conjunctiva was observed.

Section: The skin was moist and elastic. The subcutaneous fat tissue was of normal thickness. Firm adhesions were found between the pleural layers on both sides. The pleural cavities did not contain any excess fluid. The pericardial cavity is completely obliterated by adhesions. Adhesions were also present between the pericardium and the pleura. The peritoneal cavity contained a slight excess of clear amber fluid. The peritoneal surfaces were smooth and glistening throughout. The mediastinal, mesenteric and retroperitoneal lymph nodes did not show any enlargement.

Heart: The heart with pericardium and ascending aorta weighed 650 Gm. A normal amount of epicardial fat tissue was found. The coronary arteries were not thickened or tortuous. The mural endocardium was everywhere smooth and glistening. Several smooth, yellowish red thrombi were present in the right auricular appendage. A widening of the commissure occurred between the right and the left leaflet of the aortic valve. A soft, grayish, somewhat lobulated vegetation about 5 mm. in length was attached to this portion. The posterior leaflet of the aortic valve showed on its inner surface

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1. Rappaport, B. Z.: Primary Acute Aortitis, Arch. Path. 2:653 (Nov.) 1926.

several soft and friable vegetations, varying from 1 to 4 mm. in length. The leaflets in general were not thickened and did not show any retractions or adhesions to each other. The sinus of Valsalva showed a circumscribed dilatation about 1 cm. in diameter. The base of this dilated area was smooth and was apparently covered with intima. The mouths of the coronaries were slightly constricted. Only slight intimal thickening was seen in the coronary vessels, however. The mitral, tricuspid and pulmonary valves appeared normal. The mitral valve had a circumference of 10.5 cm. aortic 9 cm., pulmonic 8.5 cm. and tricuspid 14 cm. The columnae carnae on both sides were flattened. The papillary muscles were slightly hypertrophic. The myocardium on cut section was reddish-gray, soft and flabby, with an architecture somewhat coarser than the normal. The right ventricular wall measured 2 mm. in thickness, while the left measured 13 mm.

Aorta: The ascending portion of the aorta was markedly dilated, measuring 17 cm. in circumference, and it showed the wrinkling and puckering characteristic of syphilis. Several areas of hyalinization and calcification were seen, throughout. In addition, two ulcerated areas, about 2 to 3 cm. in diameter, were located in the middle of the dilated areas; they were irregularly bounded, showed ragged and slightly undermined edges and were covered with recent yellowish gray thrombi. The ulcerated areas did not show any thickening or hyalinization in their periphery. The remainder of the aorta showed areas of hyalinization and plain intimal thickening, with fatty changes throughout, and a few small, depressed, puckered scars with a bluish base.

Lungs: The right lung weighed 650 Gm.; the left, 500 Gm. Both lungs were air containing throughout.

Liver, Spleen and Kidneys: These organs were the seat of a moderate chronic passive congestion.

The remainder of the visceral organs did not show anything unusual. No permit for removal of the brain was obtained.

Histologic Observations.—In the aorta, the vasa vasorum of the adventitia showed a proliferation of endothelial cells leading in some places to a complete obliteration of the lumina. Some of the vasa vasorum were surrounded by a perivascular infiltration of lymphocytes and a few plasma cells. Several large nerve fibers in the adventitia cut on cross section did not show any changes. This is of special interest because there were several vessels visible within the sheaths of the nerve fibers that showed a marked endothelial proliferation. The nerve fibers were surrounded by a lymphocytic infiltration. There was an increase in the connective tissue of the adventitia. The outer portion of the media showed numerous young connective tissue fibers and areas of lymphocytic infiltration. Several newly formed vessels were present in this region. The entire media showed broken elastic fibers, several areas of necrosis and a somewhat diffuse infiltration of lymphocytes. The whole intima presented an increase in connective tissue and areas of hyalinization. Some of the newly formed vessels extended up to the intima and were surrounded by lymphocytes, circumscribed areas of polymorphonuclear leukocytic infiltration were observed in the inner portion of the media interrupting the course of the elastic fibers. Some of these areas reached and infiltrated the intima which was covered with recent thrombi in this region. The continuity of the intimal wall next to the lumen was broken. Spirochetes could not be demonstrated in the aortic sections by the Warthin-Starry method. Gram-Weigert staining for microorganisms in tissues gave negative results.

SUMMARY AND COMMENT

The present report concerned a case of acute suppurative aortitis, combined with syphilitic aortitis. Most of the acute lesions of the aorta were found in the aneurysmal dilatation. In addition to these changes, an acute vegetative endocarditis of the aortic valve was disclosed at autopsy. The Wassermann reaction was negative. The blood cultures showed *Diplococcus lancetolatus*. A portal of entry could not be demonstrated. It is of interest that the acute suppurative lesions of the aorta were formed exclusively in the intima and inner portion of the media, which areas are supplied not by the vasa vasorum but by the circulating blood.

THE EFFECT OF STREPTOCOCCUS CULTURE AND
OF DIPHTHERIA TOXIN ON THE
POTENCY OF INSULIN*

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It is well known that infection in diabetic patients is accompanied by an increase in the severity of the diabetes. An attack of influenza, tonsillitis or appendicitis, may produce a marked reduction in carbohydrate tolerance with considerable ketonuria and in many instances precipitate the onset of coma and death. In nondiabetic persons, Pemberton and Foster,¹ Olmstead and Gay,² Gettler and St. George³ and others have reported the occurrence of hyperglycemia or diminished carbohydrate tolerance during infections. With the introduction of insulin it has been found that larger doses are required to control the diabetes during such periods (Allen and Sherrill,⁴ Joslin,⁵ Graham⁶ and our own experience).

The suggestion has therefore been made, as an explanation of these observations, that perhaps the toxic products of infection act directly on insulin, destroying its potency. We are aware of other possibilities, such, for example, as injury by the toxins to pancreas, liver and other organs which would interfere with metabolic processes and which probably play a rôle in some cases. It is the purpose of this paper, however, to report experiments on the action of bacterial culture and of toxin on insulin.

* From the Medical Division of the Montefiore Hospital.

1. Pemberton, R., and Foster, L. G.: Studies on Arthritis in Army Based on 400 Cases; Studies on Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, *Arch. Int. Med.* **25**:243 (March) 1920.

2. Olmstead, W. H., and Gray, L. P.: Study of Blood Sugar Curves Following a Standardized Glucose Meal, *Arch. Int. Med.* **20**:384 (March) 1922.

3. Gettler, A. O., and St. George, A. V.: Blood Chemistry, *J. A. M. A.* **71**:2033 (Dec. 21) 1918.

4. Allen, F. M., and Sherrill, J. W.: *J. Metab. Research* **2**:967, 1922.

5. Joslin, E. P.: *Treatment of Diabetes Mellitus*, ed. 3, Philadelphia, Lea & Febiger, 1923, p. 98.

6. Graham, C.: *Quart. J. Med.* **18**:294, 1925.

Menten and Manning,⁷ Zeckwer and Goodell⁸ and Levine and Kolars,⁹ recognizing the part that infection plays in aggravating the metabolism in diabetes, injected various bacterial cultures into rabbits and studied the effects on the blood sugar. They found that some organisms produce a rise in blood sugar, some no change and some a slight fall. All, however, are not agreed on the last observation.

Rosenthal¹⁰ injected diphtheria toxin into rabbits. In the early stages of the intoxication in some cases there were no changes in the blood sugar, and in others there was hyperglycemia; but toward the end hypoglycemia was present. A study of the blood sugar after the administration of dextrose to some of these animals showed a diminished carbohydrate tolerance.

Tisdall¹¹ and his co-workers found a lowered carbohydrate tolerance in puppies injected with diphtheria toxin. Hector,¹² in seven cases of diphtheria, found a prolonged fall in the blood sugar following a dextrose test meal.

EXPERIMENTS

Standardization of Mice.—For testing the potency of insulin white mice were used.¹³ They were kept in wooden boxes with wire screens at top and bottom, and fed daily with rat food consisting of hominy 100 parts, rolled oats 25 parts, dried milk 16 parts, dried meat 24 parts and salt 1.5 parts, supplemented with bread, milk and lettuce. Prior to each test the animals were starved over night for a period of about eighteen hours, only water being allowed.

The mice were injected intraperitoneally with insulin and observed for over two hours for symptoms of hypoglycemia which were manifest as either paresis of the hind legs or convulsions. When a definite reaction was obtained, about 0.5 cc. of a 10 per cent solution of dextrose was injected subcutaneously, following which the animal usually recovered within a short time. Only occasionally did the animal die. Rest periods of from four to eight days were allowed, and then further tests were made. Depending on the previous reaction of the animal, the dose of insulin was increased by 0.01 unit when no effect had been observed, and decreased when the reaction was definitely positive. These tests were

7. Menten, M. L., and Manning, H. M.: J. M. Research **44**:675, 1924; J. Infect. Dis. **37**:400, 1925.

8. Zeckwer, I. T., and Goodell, H. I.: J. Exper. Med. **42**:43, 1925.

9. Levine, V. E., and Kolars, J. J.: Proc. Soc. Exper. Biol. & Med. **24**:36, 1926.

10. Rosenthal, F.: Arch. f. exper. Path. u. Pharmakol. **75**:99, 1924.

11. Tisdall, F. F.; Drake, T. G. H., and Brown, A.: Production of Lowered Carbohydrate Tolerance in Dogs, Am. J. Dis. Child. **32**:854 (Dec.) 1926.

12. Hector, F. J.: Lancet **2**:642, 1926.

13. Frazer, D. T.: J. Lab. & Clin. Med. **8**:425, 1922-1923.

repeated on each animal and are recorded separately for each group of experiments.

The tests were made at room temperature from 25 to 30 C. The mice were weighed prior to each test. The changes in weight gave us some idea of the well-being of the animals. It was apparent from the records that the variable sensitiveness of the mice to insulin was not necessarily related to differences in weight.

The preliminary standardization enabled us to use in each case approximately the smallest dose of insulin that would give a definite reaction; any marked reduction in potency would thus be detected. In the final tests comparatively large doses of culture or diphtheria toxin were mixed with the insulin so that if there were any effect on its

TABLE 1.—Results of Experiment 1*

Mouse No.	Preliminary Insulin Tests: Units of Insulin Injected						Insulin + 18 Hour Streptococcus Culture Incubated 2 Hours at 37 C.	
	0.02	0.03	0.04	0.05	0.06	0.07	Units of Insulin in Mixture Injected	Reaction
1.....	..	—	+ ± —	+ +	0.05	+
2.....	..	—	+ + +	0.03	+
3.....	..	—	±	±	+ +	0.06	+
4.....	..	—	—	—	—	+ +	0.07	—
5.....	—	—	+ +	0.05	+
6.....	..	—	+ —	+	0.05	+
7.....	..	±	+ —	±	0.05	+
8.....	..	—	+ —	+	0.05	+
9.....	—	+ —	+	0.04	—
10.....	..	—	+ +	0.04	+
11.....	..	—	+ +	0.04	+
12.....	—	+ +	0.04	+
13.....	..	±	+ +	+	0.04	+
14.....	+ —	+	0.05	+
15.....	..	+ ±	+ +	0.04	+
16.....	—	+ +	+	0.03	—
17.....	—	+ +	0.04	+
18.....	—	+ +	0.04	+
19.....	—	+ +	0.05	+

* Each sign indicates the result of a single test: +, positive insulin reaction; —, no reaction; ±, animal appears slightly ill.

potency it would be marked (10 cc. of culture to one unit of insulin; and 10 cc. of diphtheria toxin, equivalent to about 2,000 to 3,000 minimum lethal doses, to one unit of insulin). Streptococcus culture and diphtheria toxin were obtained from Dr. Krumwiede of the New York City Department of Health. According to his estimation the diphtheria toxin contained between 200 and 300 minimum lethal doses per cubic centimeter. One-fiftieth cubic centimeter killed a 450 gm. guinea-pig in two days. All the mice that received streptococcus culture mixtures were found dead the following day, and streptococci were recovered from the heart blood. The same lot of insulin was used in all the experiments.

EXPERIMENT 1.—An 18 hour old streptococcus broth culture, virulent for white mice, was mixed with insulin so that 10 cc. of culture contained one unit of insulin. This mixture (p_H 7.1) was incubated for two hours at 37 C. and then injected intraperitoneally into standardized mice. The amount injected in each case depended on the smallest dose of insulin that in the preliminary tests had been found to give a positive reaction. The results of this experiment are recorded in table 1.

EXPERIMENT 2.—Meat infusion broth was mixed with insulin so that 10 cc. contained one unit of insulin, and then inoculated with streptococcus culture. This was incubated at 37 C. for twenty-one hours and then injected intraperitoneally into standardized mice, the amounts depending on the preliminary tests (table 2).

TABLE 2.—Results in Experiment 2

Mouse No.	Preliminary Insulin Tests: Units of Insulin Injected						Streptococcus Culture Grown with Insulin for 21 Hours	
	0.02	0.03	0.04	0.05	0.06	0.07	Units of Insulin in Mixture Injected	Reaction
1.....	—	—	+	—	0.07	+
2.....	—	+	0.05	+
3.....	+	+	0.04	+
4.....	..	+	+	0.04	—
5.....	..	+	+	0.04	+
6 [*]	+	+	+	0.04	+
7 [†]	+	+	0.03	+
8.....	—	+	0.04	+

* Mouse 6 had a marked gain in weight subsequent to the tests with 0.02 unit, and since 0.03 unit gave one negative reaction, 0.04 unit was used in the test.

† Mouse 7 had a marked gain in weight during preliminary tests.

TABLE 3.—Effect of Intraperitoneal Injections of Streptococcus Culture on Blood Sugar*

Blood Sugar of Mice Receiving Culture (0.5 Cc.), Mg. per 100 Cc.	Blood Sugar of Mice Without Injection, Mg. per 100 Cc.
244	
160	190
150	170
200	
180	

* The mice were bled from two and one-fourth to two and one-half hours after injection.

CONTROLS.—Five mice were injected intraperitoneally with streptococcus culture (0.5 cc. each) without insulin, as controls, and observed for from two and one-fourth to two and one-half hours. Ill effects were not observed during this period. These mice were then killed, their throats being cut with a sharp razor. The blood was caught in tubes containing a small amount of sodium oxalate, and blood sugar determinations were made by the Folin and Wu¹⁴ method, using from 0.2 to 0.4 cc. of blood. A few mice that were not injected were killed, and their blood sugar determined. Table 3 shows the results obtained. It is obvious that the insulin reactions obtained in experiments 1 and 2 (tables 1 and 2) were not due to hypoglycemia produced by the injection of culture, since

14. Folin and Wu: J. Biol. Chem. **38**:81, 1919.

none of the animals in the control group showed any such effect (paresis, convulsions or low blood sugars).

EXPERIMENT 3.—Experiments were now made with diphtheria toxin. Mixtures (p_H 7.6) of insulin and diphtheria toxin were made so that 10 cc. of toxin contained one unit of insulin. This was incubated at 37 C. for twenty hours and then injected intraperitoneally into standardized mice (table 4).

CONTROLS.—A group of six mice injected intraperitoneally with 0.5 cc. of toxin per mouse did not show ill effects. At a later date another group of six mice, four of which were similarly injected with toxin, were killed after two hours, and the blood sugars were determined (table 5). It was obvious that hypoglycemia was not present in this group, showing that the insulin reactions recorded in table 4 were not due to toxin.

TABLE 4.—Results in Experiment 3

Mouse No.	Preliminary Insulin Test: Units of Insulin Injected						Diphtheria Toxin + Insulin Incubated at 37 C. for 20 Hours	
	0.02	0.03	0.04	0.05	0.06	0.07	Units of Insulin in Mixture Injected	Reaction
1.....	..	— + +	+	0.03	+
2.....	+ ±	+	+	0.02	+
3.....	—	— +	+	0.04	+
4.....	± +	+	+	0.02	+
5.....	—	+ +	+	0.02	+
6.....	—	+	+	0.03	—
7.....	+	+	+	0.02	+
8.....	— +	+	+	0.03	+
9.....	+	+	+ +	0.02	+
10.....	—	+ +	+	0.03	+
11.....	—	+ +	+	0.03	+
12.....	—	+ +	+	0.03	+
13.....	..	—	+ ±	0.04	—
14.....	..	+	+ —	+	0.03	+
15.....	..	+ +	+	0.03	+
16.....	—	+ +	0.04	+
17.....	+ —	+	+	0.03	+

* 0.01 did not give any reaction.

TABLE 5.—Effect of Intraperitoneal Injection of Diphtheria Toxin on Blood Sugar*

Blood Sugar of Mice Receiving 0.5 Cc. of Diphtheria Toxin, Mg. per 100 Cc.	Blood Sugar of Mice Without Injection, Mg. per 100 Cc.
108	98
103	139
93	

* The temperature of the room at the time of the experiment was 20 C.

It will be noticed that the blood sugars in the control group in table 5 are lower than those in table 3. Whether this was due to the lower temperature of the room (20 C.) at the time or to the different season of the year we cannot state. However, this does not detract from the value of the controls, since the blood sugars are approximately the same with and without toxin injections.

COMMENT

If the potency of insulin were diminished to any great extent by the culture or toxin, one would not expect to obtain insulin reactions when the "in vitro" mixtures were injected into standardized mice. However, of twenty-seven mice injected with mixtures of streptococcus culture and insulin twenty-three gave definite insulin reactions, and in seventeen mice injected with mixtures of diphtheria toxin and insulin fifteen positive reactions were obtained. From the controls in each case it is apparent that neither the culture nor the toxin injection had any tendency to produce a drop in blood sugar, nor did they produce any reactions similar to those produced by insulin. It seems to follow, therefore, that the reactions resulting from the mixtures were due to the insulin present. This belief is strengthened by the fact that the reactions were counteracted by dextrose injections.

A review of the tables shows that with the final mixtures some animals gave positive reactions with amounts that in the preliminary tests gave negative reactions, and vice versa. Thus mice 2, 5, 12, 17 and 18 in table 1, mouse 2 in table 2 and mice 5 and 16 in table 4 gave negative reactions in the preliminary tests and positive reactions with the final mixtures, whereas mice 4, 9 and 16 in table 1, mouse 4 in table 2 and mice 6 and 13 in table 4 gave positive preliminary reactions and negative reactions with final mixtures. These differences are probably due to individual variability owing to the fact that we were so close to the critical dose for each mouse.

The results do not indicate any loss in the potency of insulin when treated, as described, with diphtheria toxin or streptococcus culture.

SUMMARY

Mixtures of streptococcus culture or of diphtheria toxin with insulin incubated at 37 C. were injected into standardized mice. The results obtained do not show any appreciable loss in the potency of the insulin in such mixtures.

Laboratory Methods and Technical Notes

A SIMPLE METHOD OF TESTING FOR BLOOD COMPATIBILITY

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TECHNIC

The following method is to be employed chiefly for the direct blood matching of recipient and prospective donors preliminary to transfusion. In addition, the method may be used to obtain: (1) cells for blood grouping; (2) serum for the Wassermann test (fractional method); (3) serum or plasma for testing the patient's sensitiveness toward an otherwise compatible donor's blood.

Principle.—Blood obtained by skin puncture is drawn into capillary glass tubing which contains a few grains of dry powdered sodium citrate. After thorough mixing by gentle rotation and tipping, the lower end of the tube is plugged with wax. The tube is then allowed to stand in the upright position or, preferably, is centrifugalized. Two clearly defined layers separate: (1) red blood cells and (2) plasma. These are cross matched directly with other similarly treated blood specimens.

Materials Required.—1. Finger puncture outfit (absorbent cotton, lancet-shaped needle inserted into and through the cork of a small bottle containing 95 per cent alcohol).

2. Sterile dry capillary glass tubing (4 mm. inside diameter, cut into 10 cm. lengths).

3. Sodium citrate, chemically pure, powdered.

4. Glass slides.

5. Glass mixing rods (2 mm. diameter, cut into 10 cm. lengths).

6. Corks (no. 3; top diameter $\frac{9}{16}$ inch [1.4 cm.], bottom diameter $\frac{7}{16}$ inch [1.1 cm.]).

7. Wax pencil.

8. Known group A and B serums.

9. Small triangular file.

10. Piece of paraffin or beeswax.

Instead of an ordinary glass slide, one may use a microguide plate 2 by $4\frac{1}{4}$ inches (5 by 10.8 cm.) with 16 sq. cm. areas, the remainder of the plate being etched by sand blast (A. H. Thomas, Philadelphia, Catalogue, no. 4103). This plate or a similar device has the advantage of holding sixteen blood matchings at one time. In lieu of this plate, one may use a piece of window glass cut to about the same size and ruled off into 2 cm. squares. The known group A and B serums are not absolutely necessary, but they are useful in eliminating for direct matching all except donors belonging to the same group as the recipient. The glass mixing rod is convenient, especially if drawn out into a nipple end (cut rod into 20 cm. lengths and draw out into two equal parts in a Bunsen flame; round the pointed ends in the flame). All glassware should be clean and dry (potassium bichromate 1 part, commercial sulphuric acid 1 part, and water 10 parts is an efficient, though corrosive, cleaning fluid).

Procedure A (without preliminary grouping).—Shake a few grains of powdered sodium citrate into one of two capillary tubes. Fill both with blood obtained by finger puncture. The tube will fill quickly if the distal end is held a little lower than the patient's finger. Alternate squeezing and relaxation of the warm finger tip promotes a free flow of blood.

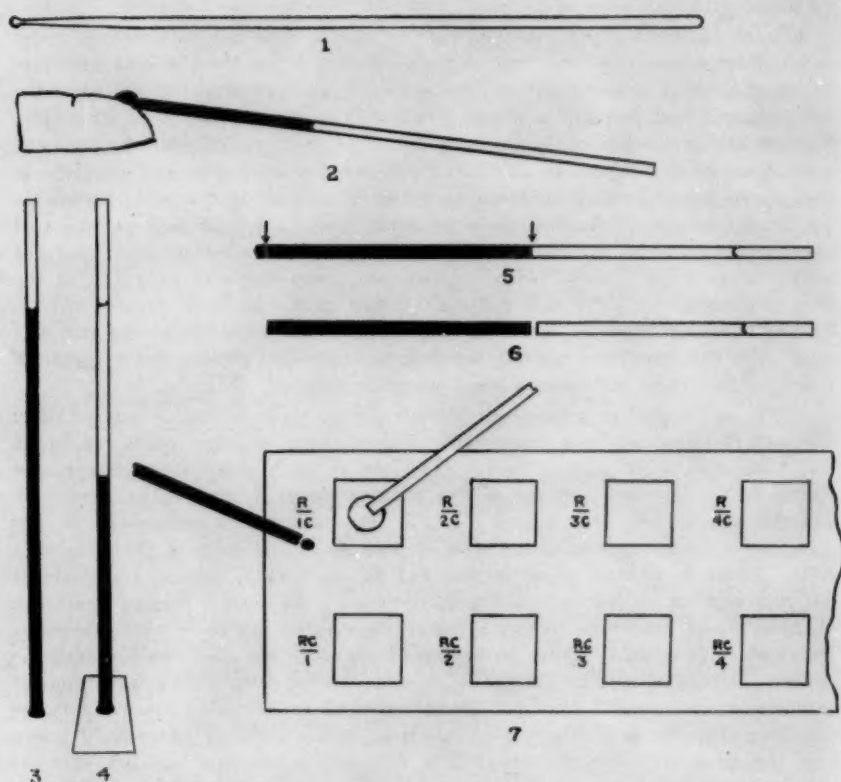
Citrate Tube: Gently rotate and tip the citrate tube twenty times in order to facilitate mixture of blood and sodium citrate. Allow the blood to gravitate to one end. Plug this end with a little softened beeswax or paraffin. Insert the tube, plugged end down, into a cork previously bored two thirds of its length. Number the corks differently for each donor (1, 2, 3, etc.). Inscribe the cork holding recipient's tube with an "R." Centrifugalize each tube at a moderately high speed for about three minutes, or allow it to stand in the upright position for twenty minutes. By this time, in most cases, the cells and plasma will have separated into two clearly defined layers. Remove the tube from the cork. Make scratch marks with file (*a*) just above the wax plug (*b*) at the line of junction of cells and plasma. Break gently at both scratch marks. Of the resulting three segments of tube discard the piece containing the wax plug. For this particular patient, one now has cells and plasma in two separate tubes. Place these tubes on a card properly labelled.

Carry out a similar procedure for each person to be tested. Thus, if there are one recipient and six prospective donors there will be seven red blood cell tubes and seven plasma tubes. Tap out of each donor tube on separate slides or on separate squares of the plate a drop of plasma, as described. Indicate source with wax pencil ("1," "2," etc., for donors, reserving "R" for recipient). In one corner of the slide or plate, tap out a drop of the recipient's cells. Using a separate clean mixing rod for each case, take up the slightest possible amount of red cells and mix thoroughly with each plasma specimen. In most cases, from one to five minutes' observation at room temperature is sufficient. Clumping is visible to the naked eye in the form of fine red sandlike grains. Detection of these clumps is often facilitated if the slide is held against a white background. A finer but usually unnecessary technic is to use a hanging drop chamber sealed with petrolatum or, if the room is excessively warm and the drop tends to dry quickly, a drop of physiologic sodium chloride solution may be added. The choice of a donor will be governed by the lack

of clumping in either cross match; i. e., $\frac{R}{1C}$ (recipients plasma against donor 1 cells) and $\frac{RC}{1}$ (recipient's cells against donor 1 plasma) do not give any agglutination. A graphic representation of the entire procedure is given.

Procedure B (with preliminary blood grouping).—In actual practice it is time-saving to ascertain the patient's blood group by preliminary test against known A and B serums, and then to cross match only bloods belonging to the same group. Preliminary blood grouping facilitates but does not eliminate direct blood matching.

Place a drop of group A and one of group B serum separately on a glass slide, using an individual glass rod for each serum. Tap a drop of red blood cells from the capillary tube on one corner of the slide. Touch lightly with a mixing rod and gently mix the cells with group A serum. Do the same for group B serum, using the same drop of blood, but a clean mixing rod. The slide is tilted and slightly rotated a few times and then allowed to stand for from one to three minutes. At the end of this period, in most cases, the



Method of testing for blood compatibility; 1, a convenient form of mixing rod; 2, method of filling the capillary tube; 3, capillary tube containing blood which has been allowed to gravitate to one end, which, in turn, has been sealed with paraffin; 4, capillary tube after centrifugalization—the clean cut separation of cells (solid black area) and plasma (clear area) should be noted; 5, division of the tube into cell and plasma units—arrows indicate the points of file scratch; 6, separated cell and plasma units—the small piece of tubing containing the paraffin plug has been discarded; 7, blood matching plate: $\frac{R}{IC}$ indicates $\frac{\text{recipient's plasma}}{\text{donor 1 cells}}$; $\frac{RC}{I}$ indicates $\frac{\text{recipient's cells}}{\text{donor 1 plasma}}$; a drop of plasma R has been tapped out of the tube directly into the ruled square and then mixed with cells (1 C) which had been previously tapped out to one side; the transfer of cells from this point to the plasma is made by means of a mixing rod.

reaction is complete. Clumping of the cells by serum is indicated by the presence of little sandlike grains, visible to the naked eye and becoming more pronounced as the drop begins to dry up.

As a basis of classification the terminology suggested by Landsteiner is used (group O when clumping does not occur in either serum, A when it occurs only in B serum, B when it occurs only in A serum and AB when it occurs in both). The letters O, A, B and AB correspond to the old Jansky numbers 1, 2, 3 and 4, and express the constitution of the corpuscles with respect to iso-agglutination.

In this connection two theoretical sources of error should be kept in mind. Guthrie and Huck¹ point to the possible existence of a C agglutinin and a c agglutinin in explanation of the occasional incompatibility of bloods belonging to the same group. Kolmer² points out the separability of agglutinins and hemolysins, agglutination not always preceding hemolysis, as was formerly generally accepted. Ottenberg³ suggests avoidance of hemolysis (a phenomenon which would interfere with agglutination) by keeping the test from the start at icebox temperature. A careful observer should not have any difficulty in detecting hemolysis in direct blood matching, as there should always be a slight turbid appearance to the drop owing to the clouding by intact red blood cells. It is rarely necessary to use the microscope.

Supplementary Applications of the Capillary Tube Method: Noncitratd Tube.—It will be remembered that originally two capillary tubes were filled with blood from each person. Thus far only the one containing sodium citrate has been utilized. The blood in the second (noncitratd) tube is allowed to gravitate to one end, that end is plugged with wax and the blood is allowed to clot in the upright position. The tube is then inserted into a properly marked cork and centrifugalized. If the clot and serum do not separate cleanly owing to adherence of the clot to the upper end of the tube, insert a fine hypodermic wire and gently loosen it up. Repeat centrifugalization. This serum, if the tube has been properly filled, will yield six drops, each equivalent to approximately 0.01 cc. Five of these may be used for a fractional Wassermann test, while the remaining drop may be injected intracutaneously into the forearm of the recipient, in order to test for serum sensitiveness to the blood of an otherwise compatible donor. The Wassermann and serum sensitiveness tests apply, of course, only to the blood of a compatible donor (i. e., one whose blood does not agglutinate in either cross match with the recipient's blood).

During the three years the capillary tube method has been in use in my laboratory, it has been shown to be open to one possible source of error. Beginners tend to use too much powdered sodium citrate. A total concentration of 0.2 per cent is sufficient to prevent coagulation. Therefore, only five or six small grains of the citrate should be used. An excess may remain undissolved and lead to erroneous clumping. This is exceedingly rare as any undissolved citrate is thrown to the bottom of the capillary tube near the wax plug and is usually removed when that portion of the tube is filed off. Then, too, a drop of physiologic sodium chloride solution (0.85 per cent), if added, will break up a citrate clump but not a true agglutination.

The method described is exceedingly simple in its application and provides all known safeguards against post-transfusion reactions.

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1. Guthrie, C. G., and Huck, J. G.: Bull. Johns Hopkins Hosp. **34**:37, 1923.
2. Stitt, E. R.: Practical Bacteriology, Blood Work and Animal Parasitology, ed. 7, Philadelphia, P. Blakiston's Son & Co., pp. 312 and 315.

**THE ADAPTATION OF ELECTRIC REFRIGERATION TO
ROOM TEMPERATURE INCUBATION ***

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Incubation at room temperature is assumed to mean from 20 to 22 C. Fluctuations of several degrees above and below this temperature are not infrequent in bacteriologic laboratories. These fluctuations in laboratory temperature render the study of those organisms that grow best at from 20 to 22 C. and those that liquefy gelatin unsatisfactory.

The only existing satisfactory arrangement for "room temperature incubation" that has come to my attention is an incubator within a brine cooled room. This equipment is awkward and expensive, and circulating brine is not always available. It occurred to my associates and me that the present day electric refrigerators might be adapted to this purpose.

We accordingly installed an M-12 Frigidaire apparatus and endeavored to raise the temperature to 22 C. by adjusting the pressure thermoregulator. It was impossible to obtain a temperature above 19.5 C. by this method, and when the laboratory was the coldest a temperature of 16 C. was reached in the refrigerator. Furthermore, there was a difference of 3 C. on the various shelves of the icebox, due, no doubt, to the sluggish convection currents within the box. These difficulties made it apparent that a constant source of heat was necessary in order to raise the temperature of the box and to improve the circulation of air within it. A 50 watt Mazda bulb was obtained and placed in the coil compartment. During six months, there has not been more than 1 degree fluctuation of temperature in this incubator, nor has there been any appreciable difference of temperature on the various shelves.

* From the Department of Pathology and Bacteriology, College of Medicine, University of Iowa.

General Review

MORPHOLOGY OF THE MESENCHYMAL REACTIONS *

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All multicellular organisms are endowed with the ability to repair damages inflicted by extraneous factors and autogenous disturbances, to resist, neutralize, digest or destroy noxious agents which endanger the normal courses of life and to eliminate them.

The connective tissue, the so-called "mesenchyme", plays the predominant rôle in these defense reactions.

After the formation of the germ layers in the vertebrate embryo, the embryonic connective tissue, the mesenchyme, appears in the spaces between these epithelium-like cell sheets. It originates from the middle germ layer, the mesoderm, through outgrowth and migration of isolated cells and cell groups. It gradually accumulates in increasing quantities between the organs of the embryo. Its distribution is mainly responsible for the outer form of the embryonic body. The epithelial structures generally keep their character of thin membranes, which cover the surface of the body, line the cavities or, through folding, give rise to glandular and other organs. The mesenchyme forms compact masses; it produces the hard supporting and protecting tissues of the skeleton and penetrates, together with the blood vessels, into all the other tissues and organs.

During its first stages of development, the mesenchyme consists of uniform spindle-shaped or stellate cells connected by processes. Then some of these fixed cells, by rounding off and isolating themselves, become wandering ameboid cells. In later stages the mesenchyme differentiates into the various types of connective tissue, as found in the adult body of the vertebrate.

The blood and its cellular elements, the blood vessels and the blood-forming organs, are also derivatives of the mesenchyme. The first endothelial cells are flattened mesenchymal cells joined by their edges to form a system of tubes. The first blood cells—the so-called primitive blood cells—are merely free, spherical mesenchymal cells floating in a liquid, the blood plasma, which is also secreted by the endothelium.

From the earliest stages of development, the cells of the blood and of the mesenchyme show the closest relationship. They can pass from the blood vessels into the tissue and vice versa. This fundamental phenomenon is observed throughout the entire life of the adult organism. Blood and connective tissue cannot be sharply separated from each other. Thus,

* From the Department of Anatomy of the University of Chicago.

in discussing the transformation of the connective tissue cells in the defense reactions, the rôle of the blood cells must also be considered.

The diffuse, loose, irregularly arranged connective tissue is the direct derivative of the original mesenchyme; it is the residue which remains more or less unchanged after the various other connective tissues have been formed. Together with the blood vessels, it forms the so-called "interstitial tissue" of the organs. It constitutes the main object of the present discussion.

The so-called "mesenchymal reactions," which seem to play an ever-increasing rôle in modern pathology, are, in fact, reactions of the diffuse connective tissue. Of course, the name "mesenchyme" in this case is not quite suitable, as this term was originally proposed as the designation of the embryonic connective tissue only.

Until recently, the only function attributed to the loose connective tissue was its mechanical rôle in the body. It certainly can be looked on as a supporting and mechanically protecting medium in which the elements of the other tissues are embedded. It fills the spaces between the organs, serving as a kind of packing material. Owing to its softness and the ease with which its parts—the fibers and the amorphous lamellae—glide over each other, it facilitates the reciprocal motility of the parts of the body.

The arrangement of the loose connective tissue in the organism and its anatomic relations to the elements of the other tissues indicate that it must play an important rôle in the nutrition of these elements. Whether some special cell types are of peculiar importance in this respect remains unknown. At any rate, all substances which exude from the blood vessels and are taken up by the cells must first pass through the endothelium and through a layer of connective tissue, however thin this layer may be. The products of the cellular metabolism, on the other hand, follow much the same path before they are carried away by the blood or lymph. The same pathway between the blood vessels and the tissue and through the layers just mentioned is also traversed by the continuous, although invisible, stream of water which proceeds in both directions during life. Thus, the connective tissue must be of great importance for the water metabolism (Petersen¹). Furthermore, it is highly probable that the cells of the loose connective tissue possess endocrine properties. The stained granules, or vacuoles, made visible in the resting wandering cells (histiocytes) by the supravital application of neutral red (Maximow²), led Renault³ to this

1. Petersen, H.: *Histologie und mikroskopische Anatomie*, München, J. F. Bergmann, 1924.

2. Maximow, A.: Ueber die Zellformen des lockeren Bindegewebes, *Arch. f. mikr. Anat.* **67**:680, 1906.

3. Renault, J.: Les cellules connectives rhagiocrines, *Arch. d'anat. micr.* **9**:495, 1907.

conception. He expressed the idea that the diffuse connective tissue must be conceived as a vast gland with internal secretion. The modern investigations on the origin of antibodies in immunity give this hypothesis substantial support.

The most important function of the connective tissue, however, seems to be its active rôle in the various "defense reactions."

Especially obvious and impressive is the rôle played by the loose connective tissue in cases in which an injurious factor of any kind acts on a localized area of the body. In such a case local reactive processes develop, which, although different according to the nature of the injury and to the region of the body, may be summarized from a general standpoint as "inflammation." Inflammation, whatever definition for this conception may be chosen, is by necessity always a function of the connective tissue, the medium surrounding and supporting the other elements of the body.

Even in the normal organism, solid or soluble endogenous foreign substances, especially those formed through the decomposition of proteins, may arise in various places and cause the connective tissue elements to react, to resorb and to dispose of these impurities ("physiologic inflammation"—Rössle⁴).

The injurious stimulus exerted by the exogenous foreign substance or body in the true "pathologic" inflammation naturally provokes a far more intense local defense reaction, which consists of a series of highly complex processes. Local connective tissue cells and cells of the blood and the wall of the blood vessel, as will be seen, are equally involved, and an important rôle is also played by the vasomotor nerves. The goal is reached partly through phagocytosis, storing and intracellular transformation of the foreign bodies, and partly through the action of substances secreted by connective tissue or blood cells. According to Rössle,⁴ the essential nature of this process is always a parenteral digestion of foreign substances by the connective tissue. In the later stages, an additional phenomenon—the formation of an isolating capsule surrounding the foreign body—may help to combat and to isolate the injurious agent.

In lesions of a generalized nature, in which foreign or toxic substances or infectious agents of any kind are distributed over the whole organism, the diffuse connective tissue, together with the blood, the blood-forming organs and the vascular system, again has to take care of the defense reaction and of the restoration of normal conditions. Their activity in this case is also aimed at the quickest possible disposal of the foreign noxious factors and at the cleansing of the body by means of neutralization of the toxins, destruction of the micro-organisms and similar functions.

4. Rössle, R.: Referat über Entzündung, Verhandl. d. deutsch. path. Gesellsch. 19:18, 1923.

The morphologic manifestations of inflammation are relatively easy to follow, but the study of the morphology of the nonlocalized, general defense phenomena, as observed in infections, in intoxications, in experiments with parenteral introduction of foreign substances, especially proteins, and under other conditions, offers much greater difficulties.

The so-called constitution, the endogenous individual peculiarities of an organism which manifest themselves under both physiologic and pathologic circumstances and especially in the course of inflammatory processes and of general infections, seems also to depend mostly on the qualities of the "mesenchyme" (Sauerbruch,⁵ Rössle,⁶ Bogomolez,⁷ Alexeieff⁸ and others). The changes of the organism in cases of allergy are probably also largely connected with corresponding alterations in the diffuse connective tissue (Gerlach⁹ and others).

When tumors develop, the fate of the blastoma is influenced to a high degree by the general properties of the loose connective tissue and by its reactions to the tumor cell. When malignant tumors are experimentally inoculated into immune animals, certain reactive processes on the part of the local connective tissue cells and of the hematogenous leukocytes can be noticed microscopically (Da Fano,¹⁰ Dantschakoff¹¹ and others). Murphy¹² and his collaborators believe that the lymphoid elements play an especially important rôle in this connection. On the other hand, in cases in which the inoculated carcinoma "takes," the local connective tissue furnishes the stroma for the tumor, and thus the connective tissue and the epithelial elements are both combined into a new tissue unit.

The fundamental processes in all mesenchymal reactions are, of course, chemical. However, as the apparatus in charge of these func-

5. Sauerbruch, F.: Zelluläre Abwehrvorgänge und ihr Ausdruck im Parabioseversuch, München. med. Wchnschr. **70**:866, 1923.

6. Rössle, R.: Die konstitutionelle Seite des Entzündungsproblems, Schweiz. med. Wchnschr. **53**:1053, 1923.

7. Bogomolez, A.: Constitution and Mesenchyme, Publications of the Path. Laboratory of the University of Saratow, 1 (Russian). Review, Centralbl. f. allg. Pathol. u. path. Anat. **35**:375, 1924.

8. Alexeieff, A.: Rôle physiologique des lymphocytes. Théorie du mésenchyme, Compt. rend. Soc. de biol. **93**:496, 1925.

9. Gerlach, W.: Studien über hyperergische Entzündung, Virchows Arch. f. path. Anat. **247**:294, 1923.

10. Da Fano, C.: Zelluläre Analyse der Geschwulstimmunitätsreaktionen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **5**:1, 1910.

11. Dantschakoff, W.: Digestive Activity of Mesenchyme: A. The Ehrlich Sarcoma Cells as Object, Am. J. Anat. **29**:431, 1921.

12. Murphy, J., and Nakahara, W.: The Lymphocyte in Natural and Induced Resistance to Transplanted Cancer: V. Histological Study of the Lymphoid Tissue of Mice with Induced Immunity to Transplanted Cancer, J. Exper. Med. **31**:1, 1920.

tions is diffusely spread all over the body, investigation with the aid of only chemical methods encounters great difficulties. The blood serum is generally used as material for immunologic and serologic research; but this liquid is merely a small part of the body liquids, which are the arena of the immunity reactions and which cannot be easily collected for examination. The microscopic study furnishes the only visible basis for the understanding of the mesenchymal reactions.

A thorough knowledge of the normal constituent parts of the connective tissue and the blood and of the development and extremely complex genetic relationship of the elements of these tissues in different species of animals is necessary for the successful elucidation of the morphology of the defense phenomena. A faultless technic is also a self-evident and unavoidable requirement.

CELL TYPES OF CONNECTIVE TISSUE AND BLOOD

From a general histophysiologic point of view, three vast groups of cells can be distinguished in the connective tissue and the blood of vertebrates:

1. Fixed, highly differentiated cells, which produce the fibrous intercellular substance in the connective tissue and the plasma in the blood. They may be designated as fibrocytes. These elements are represented in the vascular system by endothelial cells and in the connective tissue by fibroblasts or fibrocytes. The same cells are present in cartilage and bone as cartilage and bone cells, respectively.

2. Fixed or free elements, which possess a marked ability for phagocytosis and vital staining. They readily resorb and store various substances, especially those of colloidal nature. They play an important rôle in the intermediate metabolism of the body and especially in the various defense processes. They are generally designated as histiocytes (Goldmann,¹³ Tschaschin,¹⁴ Kiyono¹⁵ and Aschoff¹⁶). They may assume different characters in various parts of the body, through

13. Goldmann, E.: Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," I. Beitr. z. klin. Chir. **64**: 192, 1909; Studien zur Biologie der bösartigen Neubildungen, Beitr. z. klin. Chir. **72**:1, 1911; Neue Untersuchungen über die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," Beitr. z. klin. Chir. **78**:1, 1912.

14. Tschaschin, S.: Ueber die "ruhenden Wanderzellen" und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphozyten, Folia haemat. **17**:317, 1913.

15. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

16. Aschoff, L.: Das reticulo-endotheliale System, Ergebn. d. inn. Med. u. Kinderh. **26**:1, 1924; Morphologie des reticulo-endothelialen Systems, Handbuch der Krankheiten des Blutes und der blutbildenden Organe, edited by A. Schittenhelm, Berlin, Julius Springer, 1925, vol. 2, p. 473.

adaptation to special local structural and functional conditions. Their fundamental properties and potencies of development are probably everywhere identical. In the common loose or dense irregularly arranged tissue, as well as in the serous membranes and especially in the omentum, they are known as macrophages (Metchnikoff,¹⁷ Evans¹⁸), as clasmatoocytes (Ranvier¹⁹), as resting wandering cells (Maximow²), as rhagiocrine cells (Renaut³) and as adventitial cells (Marchand²⁰). In the lymphoid and myeloid tissues and in the red pulp of the spleen, they have been known for a long time as reticular cells. In the liver they line the intralobular capillaries as the stellate cells of von Kupffer.²¹ Similar elements are found in the wall of the venous capillaries in the suprarenal and in the hypophysis. It has to be added that in the lymph nodes, the bone marrow and the spleen, the lymph sinuses and the venous sinusoids are lined by modified, flattened histiocytes, which are sometimes described as "endothelium," although they are different in their structure and behavior from the true endothelium, which belongs to the group of fibrocytes. An adequate name for all these histiocytes lining lymph or blood channels might be the term "littoral cells" ("Uferzellen"), as proposed by Siegmund.²² They should be sharply discriminated from the endothelium of the common blood vessels.

3. Hemocytes, which are free cells, circulating in the blood and lymph and accumulating in the blood-forming organs. Among them should be distinguished (a) undifferentiated elements—the so-called hemocytoblasts, which are the common stem cells for the other hemocytes, and (b) specifically differentiated elements, originating from the hemocytoblasts—the granulocytes (granular leukocytes of three types, eosinophilic, basophilic and special), the erythrocytes and the megacaryocytes.

As is well known, two main theories of hemopoiesis exist in modern morphologic hematology, the unitarian and the dualistic. The dualistic theory discriminates sharply between the stem cell of the lymphoid tissue on the one hand, known as the lymphoblast, and the myeloid tissue on the other hand, known as the myeloblast, while the unitarian theory is that these cells are not only histologically similar, but identical in their

17. Metchnikoff, E.: *Leçons sur la pathologie comparée de l'inflammation*, Paris, Masson & Cie., 1892.

18. Evans, H.: *The Macrophages of Mammals*, *Am. J. Physiol.* **37**:243, 1915.

19. Ranvier, L.: *Des clasmatoocytes*, *Arch. d'anat. micro.* **3**:123, 1900.

20. Marchand, F.: *Ueber die bei Entzündungen in der Peritonealhöhle auftretenden Zellformen*, *Verhandl. d. deutsch. path. Gesellsch.* **1**:63, 1898.

21. Kupffer, C. v.: *Ueber die sogenannten Sternzellen der Säugetierleber*, *Arch. f. mikr. Anat.* **54**:254, 1899.

22. Siegmund, H.: *Reizkörpertherapie und aktives mesenchymatisches Gewebe*, *München. med. Wehnschr.* **70**:5, 1923.

prospective possibilities. Recent investigations, especially of experimental nature, seem to corroborate the unitarian theory. Thus, the hemocytoblasts as found, for instance, in the bone marrow, are identical with lymphocytes, as found in the lymphoid tissue. The lymphocytes, under suitable circumstances, are able to produce all kinds of myeloid elements of the blood.

In the normal adult organism, the consumption of cells in the connective tissue is small, and therefore their neoformation also is insignificant. In this passive, resting condition, the developmental potencies of the cells for the most part remain latent, and their mutual relations are not clearly manifest. The cells of the blood seem to be independent of the cells of the connective tissue. In pathologic conditions this may change considerably, when the elements of the blood and connective tissue become active and display their prospective potencies.

The reaction of the connective tissue and blood to noxious stimuli is the most common and typical case of releasing the dormant developmental and functional possibilities of the elements of these tissues. The phenomena in the local defense reaction, i. e., the inflammation, are especially easy to survey and to follow in their various stages.

LOCAL DEFENSE REACTION: INFLAMMATION

The structure of the connective tissue in an area of inflammation undergoes deep changes. In the various types of inflammation—aseptic, caused by a clean wound or a sterile foreign body; purulent, caused by special micro-organisms; acute, chronic and other forms—the individual phenomena composing the complex process may show innumerable variations. The cellular types and their transformations are always the same in principle. ✓

A. Cell Types Involved in the Inflammatory Reaction.—On the field of inflammation three principal types of cells can be distinguished (Maximow²³): ✓

1. The fibroblasts, which are the "common" connective tissue cells. These cells seem not to play an appreciable rôle in the defense reaction

23. Maximow, A.: Experimentelle Untersuchungen über entzündliche Neubildung von Bindegewebe, Beitr. z. path. Anat. u. z. Pathol., Supp. 5:1, 1902; Weiteres über Entstehung, Struktur und Veränderungen des Narbengewebes, ibid. 34:153, 1903; Ueber entzündliche Bindegewebsneubildung bei der weissen Ratte und die dabei auftretenden Veränderungen der Mastzellen und Fettzellen, ibid. 35:93, 1904; ibid. Beiträge zur Histologie der eiterigen Entzündung, ibid. 38:301, 1905; Ueber entzündliche Bindegewebsbildung beim Axolotl, ibid. 39:333, 1906; Die Histiogenese der Entzündung (Mit Berücksichtigung der gewebsebildenden hämatogenen Zellen), Verhandl. d. 16 Internat. Med. Kong. zu Budapest, 1909, sect. 4b, p. 41.

proper, except in the later stages, when, as has been mentioned, they provide a fibrous capsule isolating a foreign body, an old abscess or foci infected by micro-organisms. Their principal rôle is regenerative; in the healing of a wound they produce the new connective tissue to fill out the defect. They gradually replace the cavity of an old resorbed abscess and penetrate into the free spaces of any foreign body introduced into the tissue. In chronic productive inflammation their neoformation may diffusely increase the present quantity of interstitial tissue which replaces the degenerating parenchymatous elements of an organ. The result in this case is induration.

The fibroblasts are relatively slow to react to the inflammatory stimulus. In acute inflammation they slowly swell and shorten their spear-shaped processes during the first fifteen or twenty hours. After about fifteen hours, the first mitotic divisions appear, and in this way the neoformation of connective tissue starts; its intensity and duration are entirely dependent on the nature of the inflammatory stimulus, the region of the body and the constitution of the organism. In late stages they gradually elaborate fibrous intercellular substance, collagen and eventually elastin and networks of reticulin and thus form scar tissue.

In his recent papers, von Möllendorff²⁴ laid much stress on the syncytial nature of the fibroblastic network. This assumption can be neither proved nor denied. It is well known that the fibroblasts are connected with each other by means of their spear-shaped processes. Whether the character of this connection is true fusion of the protoplasm of the individual cells or merely intimate contact cannot be decided. At any rate, many fibroblasts at once appear in inflammation, as well as in tissue cultures, and glide about as isolated spindle-shaped or stellate elements.

The only conclusively demonstrated mode of proliferation of the fibroblasts is mitosis. The existence of amitosis has been repeatedly claimed by various investigators. Recently, von Möllendorff,²⁴ Koll²⁵ and Knake²⁶ again laid special stress on this type of division. They expressed the belief that the fibroblasts at the beginning of inflammation undergo extremely rapid amitotic divisions, and that this is the explanation of the almost instantaneous flooding of the tissue with innumerable

24. Möllendorff, W., and M. v.: Das Fibrozytennetz im lockeren Bindegewebe, seine Wandlungsfähigkeit und Anteilnahme am Stoffwechsel, *Ztschr. f. Zellforsch. u. mikr. Anat.* **3**:503, 1926; Die örtliche Zellbildung in Gefässwänden und im Bindegewebe, *München. med. Wchnschr.* **73**:135, 1927.

25. Koll, W.: Bindegewebsstudien: II. Die Wirkung von Patentblau auf das Unterhautbindegewebe der Maus, *Ztschr. f. Zellforsch. u. mikr. Anat.* **4**:702, 1927.

26. Knake, C.: Bindegewebsstudien: III. Die Histio- und Leukozyten-Entstehung bei Tuschewirkung auf das lockere Bindegewebe des Kaninchens, *Ztschr. f. Zellforsch. u. mikr. Anat.* **5**:1, 1927.

new cells of various types. I have never been able to convince myself of the existence of amitosis as a method of true cell multiplication in inflammation, and my new experiments again corroborate this negative view. The nuclei of the fibroblasts sometimes show folds and constrictions on their membrane, but a division of the nucleus need not follow. At any rate, it is impossible to see anything like a division of the cell body. It is certain that a faulty technic is responsible for these unusual observations of von Möllendorff.

2. The special (polymorphonuclear) leukocytes (the neutrophils in the human organism). These elements are especially typical for every kind of inflammation. Under strictly physiologic conditions they seem to be confined to the interior of the blood vessels and to the myeloid tissue and are not found anywhere in the connective tissue. They are the first to appear on the field of inflammation. While they are not numerous in aseptic inflammation and soon disappear, in suppuration their number in the tissue rapidly increases, and they form the pus corpuscles.

It is certain that the special granular leukocytes play an important rôle, combating in various ways the injurious inflammatory agent. The visible manifestation of this is phagocytosis exerted especially toward micro-organisms; these cells were called microphages by Metchnikoff. The phagocytosed bacteria are digested intracellularly and destroyed. In many cases, however, the phagocytosis fails to reach its aim, for the bacteria may multiply in the interior of the cells with a resultant spreading of the infection. A more important way in which the special leukocytes fulfil their destiny on the field of inflammation is the discharge of various substances which are supposed to act on the factor causing inflammation. Some of these substances may perhaps be secreted by the living cells. Most of them, however, become available only after the destruction of the cell. The special leukocytes are supposed to furnish bactericidal substances and to neutralize and detoxicate certain toxins of bacterial origin. Their proteolytic and oxydizing enzymes must also be of importance for the protective functions of these cells.

It is an established fact that the polymorphonuclear special leukocytes are unable to multiply or to transform themselves into other types of cells. The idea expressed by Lewis,²⁷ that the special leukocytes in aseptic inflammation in the rat transform themselves into macrophages, contradicts the fundamental conceptions of modern hematology

27. Lewis, W. H.: On the Possibility of the Transformation of Polymorphonuclear Leucocytes into Mononuclears, Epithelioid Cells and Macrophages in Cultures of the Buffy Coat of the Blood of the Rat, *Am. A. Anat.*, 42d Session, New Haven, *Anat. Record* 32:216, 1926.

and pathology. After a longer or shorter stay in the field of inflammation, the special leukocytes always degenerate and disappear. A few may perhaps be carried away by the blood or lymph stream.

The other types of granular leukocytes—the eosinophils and basophils—appear in inflamed tissue but rarely, and then only in special cases (Hodgkins' disease, allergic inflammation and similar conditions).

3. The third cell type found in the inflamed tissue is a motile, phagocytic cell varying in size, without specific granulations in the protoplasm and with a simple round, oval or kidney-shaped, nonpolymorphous nucleus. They have been called "macrophages" by Metchnikoff¹⁷ because their phagocytic activity is usually directed toward larger particles, dead cells, foreign bodies of every kind and similar substances. However, they also readily phagocytose certain bacteria, for instance, tubercle bacilli.

These "mononuclear exudate cells," as they are sometimes called, appear in the inflamed area in numerous forms, from the smallest cells that look like lymphocytes, and medium-sized cells that remind one of monocytes, up to huge cell bodies with abundant protoplasm and inclusions. They can transform themselves in the further course of inflammation into epithelioid cells of an extremely varying aspect, such as epithelioid cells of the tubercle, into pus phagocytes in old abscesses (Maximow²⁸) and other forms. In the presence of larger solid foreign bodies, they fuse together and produce multinucleated giant cells. The plasma cells, which appear in certain cases of inflammation, especially in later stages, may also be looked on as belonging to this group. Because of this highly polymorphous character and the ability to undergo various structural modifications, I²⁸ termed these cells "polyblasts."

The polyblasts, the mononuclear exudate cells, are doubtless the most important factors in the inflammatory defense reactions. After the special leukocytes, which appear first, have done their work, the polyblasts, gradually increasing in numbers, display great energy in removing the cause of the inflammatory irritation and in cleansing the tissue of the various debris. They engulf and digest all kinds of useless and obnoxious material accumulated in the tissue—dead cells, micro-organisms and various particulate substances. It is certain that for this purpose they also can elaborate enzymes and other soluble substances. Contrary to the behavior of granular leukocytes, the polyblasts as a rule do not disintegrate in order to free these products of their metabolism, but secrete them. Whenever the polyblasts are found adjacent to the surface of large necrotic masses (for instance, muscle fibers or old pus) or to digestible, but solid foreign bodies which are too large to be engulfed by the cell body, they are seen dissolving the material wherever

28. Maximow (footnote 23, fourth reference).

their protoplasm touches it, penetrating into it and breaking it up into smaller particles.

Only a small part of the polyblasts degenerate. Most of them remain in the tissue when the inflammation subsides. They are transformed into resting, nonmotile, usually fusiform or branched cells which are similar to the normal resting wandering cells. They remain scattered among the fibroblasts of the newly formed granulation and scar tissue. In later stages, many of them may gradually acquire the structure of common fibroblasts (Maximow²⁹).

B. Origin and Genetic Relationships of the Cells of the Inflamed Tissue.—(a) Fibroblasts: The origin of the new fibroblasts in the inflamed area is obvious—they are the progeny of the preexisting local elements of the same kind; only a small part of them may arise from the endothelium of the small vessels, the capillary veins (Maximow²⁸).

My investigations, carried out especially on the loose subcutaneous and intermuscular tissue of the rabbit, have led to the conclusion that the fibroblasts are highly differentiated cells. When they proliferate in response to the inflammatory stimulus, they may considerably contract and partly withdraw their typical processes. At the height of the mitosis, they may temporarily become completely round. In the telophase, however, the spear-shaped processes reappear, and the original form is restored. They are never transformed into true ameboid elements, although a more or less complete rounding off may occur sometimes. Exclusive of this appearance during mitosis, the nucleus always keeps its typical structure of a delicately outlined oval body with dustlike chromatin and distinct nucleoli.

(b) Special (Polymorphonuclear) Leukocytes: For many years it has been believed that the source of these cells on the field of inflammation lies in the blood leukocytes which have migrated from the blood vessels and have been attracted by chemotactic, osmotic or electrotropic influences. It is true that the exact nature of the factors regulating this phenomenon remains unknown, but the fact itself seems well established. These cells, as has been mentioned, are absent in the connective tissue under physiologic conditions, but are numerous in the blood. They appear at once in large and rapidly increasing numbers at the very beginning of inflammation. They all look like the leukocytes in the blood stream. No transitions can be found between them and the local elements. Furthermore, it is easy to see their accumulation in the smaller vessels, especially in the capillary veins, and their massive migration through the walls of the latter, in fixed preparations as well as in

29. Maximow (footnote 23, first reference).

suitably chosen living specimens, for instance, in the mesentery of the frog, as was first shown by the famous experiment of Cohnheim.³⁰

It is difficult to understand why a confirmation of the experiment of Cohnheim, which long since became a class demonstration, should be necessary. Nevertheless, some recent investigators seem to have lost confidence in the correctness of these concepts. The paper of Westphal³¹ brought the confirmation of Cohnheim's observations without adding much to the previous knowledge of this phenomenon. Kauffmann,³² on the contrary, using the same material (frog's mesentery) as Cohnheim did, completely denied the existence of migration and believes that the cells which appear in the tissue originate exclusively from the "adventitial cells."

The explanation of these discrepancies is given by the lack of experience of the respective authors in the histologic discrimination of the different types of cells, by their disregard of the literature on the subject and by the inadequacy of the methods they used in their work. This is especially striking in the case of Kauffmann, whose extremely vague and confused description is dominated by the preconceived idea of the exclusive participation of Marchand's adventitial cells in the production of the inflammatory exudate cells.

Von Möllendorff²⁴ and his students, Koll²⁵ and Knake,²⁶ in a series of papers, recently came to the most unexpected and unusual conclusions regarding the morphology of the local inflammatory mesenchymal reaction in general and the origin of the polymorphonuclear special granulocytes in the inflamed areas in particular.

These investigators injected colloidal solutions of various degrees of dispersion—trypan blue, "Patentblau" or India ink—into the subcutaneous tissue of mice and rabbits. As a response to this intrusion they describe a rapid breaking up of the fibroblastic "syncytium" into free cells with the character of macrophages or polyblasts and of polymorphonuclear eosinophil and special leukocytes. These transformations were accomplished in the course of a few hours and were accompanied by an intense amitotic proliferation of the fibroblasts. The slender spear-shaped processes of the fibroblasts were withdrawn, and the cells were rounded off and became free and independent of each other. The nucleus showed constrictions and (in the rat) acquired a ring-shaped form. Simultaneously, granules appeared in the cytoplasm. My experiments² have shown that in the adult mouse

30. Cohnheim, J.: Ueber Entzündung und Eiterung, Virchows Arch. f. path. Anat. **40**:1, 1867.

31. Westphal, U.: Eine Nachprüfung des Cohnheim'schen Entzündungsversuches (Ein Beitrag zur Emigrationslehre), Frankfurt. Ztschr. f. Path. **30**:1, 1924.

32. Kauffmann, F.: Eine Nachprüfung des Cohnheim'schen Entzündungsversuches, Frankfurt. Ztschr. f. Path. **24**:183, 1920.

eosinophilic leukocytes with ring-shaped nuclei are a normal constituent part of the loose connective tissue and that they must have migrated from the blood vessels. Von Möllendorff, on the contrary, believes that the eosinophilic leukocytes originate from fibroblasts. Later these elements are transformed into special leukocytes (with a highly polymorphous, ring-shaped nucleus) and finally into nongranular leukocytes.

These observations of von Möllendorff and his collaborators are presented arbitrarily, without discussing the totally different results of other authors. They seem to revolutionize completely the dominant ideas on the morphology of the local defense reactions, as represented, for instance, in my work²³ or in that of Marchand.²⁴ They also disregard the classic conceptions on the origin and development of granular leukocytes.

A successful overthrow of generally accepted doctrines has always been accomplished either by the use of completely new, unusual material for investigation or by the application of new experimental methods to familiar objects. Neither is the case in the investigations of von Möllendorff. As material he used the common, loose, irregularly arranged connective tissue of the mouse or of the rabbit—a tissue thoroughly studied and minutely described by numerous antecedent investigators. His methods were the simplest. He used as local irritation subcutaneous injections of acid aniline dyes or India ink—a procedure also commonly used in class work. He did not apply to the study of the tissue reaction the modern supravital method with neutral red (Maximow,² Renaut,³ Simpson,³⁴ Sabin³⁵ and others). He merely fixed small membranes of the spread tissue in a 10 per cent solution of formalin and stained with iron hematoxylin. He modified the technic of this stain slightly and, instead of using the mordant and the hematoxylin solution separately, mixed them and stained at 56 degrees for ten minutes. It is clear that this procedure cannot give pictures which had not been seen by previous workers.

Control experiments with the use of von Möllendorff's own technic have recently been performed in my laboratory. It was possible to compare their results with a series of original slides of von Möllendorff, which he sent me. New facts could not be discovered. After the subcutaneous injection of trypan blue or India ink, the familiar pictures

33. Marchand, F.: *Der Prozess der Wundheilung*, Deutsche Chirurgie, edited by v. Bergmann and v. Bruns, Stuttgart, 1901; *Die örtlichen reaktiven Vorgänge (Lehre von der Entzündung)*, Handbuch der allgemeinen Pathologie, edited by L. v. Krehl and F. Marchand, Leipzig, S. Hirzel, 1924, vol. 4, part 1, p. 78.

34. Simpson, M.: The Experimental Production of Macrophages in the Circulating Blood, *J. M. Research* **43**:77, 1922.

35. Sabin, F.: Studies of Living Human Blood Cells, *Bull. Johns Hopkins Hosp.* **34**:277, 1923.

of inflammatory reaction to a soluble or a particulate foreign substance were found. Nothing could be revealed concerning the leukocytes which would suggest the possibility of their origin from the fibroblasts. Even on poorly stained slides the differences between these two types of cells are striking, and they have nothing in common. The fibroblasts are large stellate, fusiform or angular bodies with processes and a large oval nucleus. The leukocytes have small, sharply outlined, ameboid cell bodies with specific granules and a polymorphous nucleus. Transitional forms could not be detected. The original slides of von Möllendorff proved to be heavily overstained (or insufficiently differentiated) and in many places showed mere black silhouettes of cell bodies. No trace of amitotic division of the fibroblasts could be found, nor any indication of a rounding up of the cell body of the fibroblasts, of their shrinkage to small round cells or of the elaboration of special granules.

The accumulation of the leukocytes in the tissue starts immediately after the injection of the foreign substance and increases rapidly; these cells appear at once as foreign elements which show no relation whatever to the local elements.

Von Möllendorff completely disregards the possibility of migration of granular leukocytes out of the blood vessels. As he confined himself to the study of small particles of connective tissue, stretched on slides, he naturally could not observe this phenomenon. When small particles of the loose tissue are cut out, the vessels in which the emigration takes place remain on the surface of the fascia, of the skin or other parts from which the tissue has been removed. Only sections give the opportunity to see the emigration on fixed material. Any section of von Möllendorff's material containing blood vessels certainly would have shown him the real origin of the leukocytes.

It is interesting that coincidentally with the publications of von Möllendorff concerning the origin of granular leukocytes in the local reactive processes, Oeller,³⁶ Töppich³⁷ and Siegmund³⁸ have come to similar conclusions about the origin of granulocytes in general defense reactions. They claim to have found, after injection of antigen (foreign erythrocytes) or tubercle bacilli into the veins of sensitized or infected animals (guinea-pigs), an intense neoformation of granulocytes from the endo-

36. Oeller, H.: Die funktionelle Bedeutung der Gefässwandzellen bei akuten Infektionen, *M. Klin.* **19**:97, 1923; Experimentelle Studien zur pathologischen Physiologie des Mesenchyms und seiner Stoffwechselleistungen bei Infektionen, *Krankheitsforschung* **1**:28, 1925.

37. Töppich, G.: Die zellulären Abwehrvorgänge in der Lunge bei Erst- und Wiederinfektion mit Tuberkelbazillen, *Krankheitsforschung* **2**:15, 1925.

38. Siegmund, H.: Untersuchungen über Immunität und Entzündung, *Verhandl. d. deutsch. path. Gesellsch.* **19**:114, 1923.

thelium of the blood capillaries of the lungs. It is believed that the process develops with extreme rapidity (in the course of minutes) and consists chiefly in amitotic proliferation. These sensational communications have met severe criticism (Schilling,³⁹ Seemann,⁴⁰ Gerlach and Finkeldey⁴¹) and could not be confirmed in my laboratory.

(c) Eosinophilic Leukocytes: The much debated question of the so-called local eosinophilia is closely related to the problem under consideration. The accumulation of eosinophilic cells in tissues which normally do not contain them may be looked on as the visible manifestation of a slow, chronic defense reaction of the tissue against a specific irritating factor. The eosinophils seem to play a prominent rôle in the resorption of the products of parenteral protein decomposition, and therefore are conspicuous in all kinds of local and general anaphylactic reactions. It is probable, furthermore, that the eosinophilic leukocytes represent one of the methods of defensive reaction used by the organism against bacterial and parasitic infections. Their presence in the diffuse connective tissue of certain species of animals (guinea-pig, rat and mouse) in apparently normal conditions will perhaps also find its explanation in some kind of chronic infection (worms) or parenteral intoxication. At least, the cells in question are never found in the connective tissue of the embryo and gradually accumulate in postembryonic life.

In the overwhelming majority of all cases of local (and general) eosinophilia, the eosinophils are represented by common eosinophilic leukocytes which have migrated from the vessels, probably guided by chemotactic influences and gradually accumulated in the tissue (Maximow,² Schwarz,⁴² Huber and Koessler,⁴³ Marchand⁴⁴). The cells always contain a typical bilobed or ring-shaped nucleus. Only in some special regions, as in the tunica propria of the intestinal mucosa, the presence of eosinophils with a compact, oval, sometimes mitotically dividing nucleus seems to indicate their true local origin. In these cases, however, the local eosinophilic leukocytes can be traced back to the embryonic period, when small granulopoietic foci are occasionally found scattered all over the body. However, even the advocates of a local

39. Schilling, V.: Das Knochenmark als Organ, *Deutsche med. Wchnschr.* **51**:261, 344, 467 and 516, 1925.

40. Seemann, G.: Zur Biologie des Lungengewebes, *Beitr. z. path. Anat. u. z. allg. Pathol.* **74**:345, 1925.

41. Gerlach, W., and Finkeldey, W.: Zur Frage mesenchymaler Reaktionen. Die Beteiligung der Lunge an den Abwehrreaktionen des normalen und leistungsgesteigerten Organismus, *Verhandl. d. deutsch path. Gesellsch.* **21**:173, 1926.

42. Schwarz, E.: Die Lehre von der allgemeinen und örtlichen "Eosinophilie," *Ergebn. der allg. Path. u. path. Anat.* **17**:137, 1914.

43. Huber, H., and Koessler, K.: The Pathology of Bronchial Asthma, *Arch. Int. Med.* **30**:689 (Dec.) 1922.

44. Marchand (footnote 33, second reference).

origin of the eosinophilic cells in the connective tissue do not claim that they originate from fibrocytes in the sense of the new theory of von Möllendorff, but from indifferent wandering cells.

The idea of the transformation of the eosinophils into special granular leukocytes and later into nongranular leukocytes, as expressed by von Möllendorff, contradicts the fundamental conceptions of the genetic relationships of the specific myeloid blood cells and of their development in the blood-forming organs. In any case of inflammation, provided suitable technic is used, it is easy to demonstrate that there are no relations between the eosinophils and the special leukocytes. The nongranular leukocytes of von Möllendorff are artefacts caused by deficient technic.

It may be mentioned that Feringa⁴⁵ claims to have found transformation of lymphocytes, which migrated from the blood vessels in the peritoneal wall after intraperitoneal injections of indifferent liquids into granular myelocytes and leukocytes. Although the lymphocytes possess hemopoietic abilities, Feringa's observations cannot be considered as bringing evidence in favor of this thesis.

Thus, the classic conceptions of the origin of the granular leukocytes on the field of inflammation need not be modified.

(*d*) Basophilic Leukocytes and Mast Cells: The rôle of the cells with basophilic granules in the local defense reactions is obscure. In animals possessing numerous basophilic leukocytes in the circulation these cells sometimes migrate into inflamed foci (Maximow⁴⁶). The connective tissue mast cells (in the rat) are shown to be phagocytosed and destroyed by polyblasts in the early stages of acute inflammation (Maximow⁴⁶).

(*e*) Polyblasts (Mononuclear Exudate Cells, Inflammatory Macrophages): The question of the origin of the polyblasts on the field of inflammation, their relation to the other connective tissue cells and to the leukocytes and their potencies of development have been the subject of numerous discussions. There was a time when Ziegler⁴⁷ believed that they originate exclusively from leukocytes migrating from blood vessels. Later, in the nineties of the preceding century, the other extreme theory, the exclusive origin of the exudate cells from the common fibroblasts, seemed to gain a decisive victory (Ziegler,⁴⁸

45. Feringa, K.: Ueber die Ursachen der Emigration der Leukocyten. III. Die Herkunft der Exsudatleukocyten, *Pflügers Arch. f. d. ges. Physiol.* **200**:159, 1923.

46. Maximow (footnote 23, third reference).

47. Ziegler, E.: Untersuchungen über die Herkunft der Tuberkel-Elemente, 1875; Ueber die pathologische Gewebs- und Gefäßneubildung, Würzburg, Standinger, 1876.

48. Ziegler, E.: Ueber die Beteiligung der Leukocyten an der Gewebsneubildung, *Verhandl. d. X. Internat. Med. Cong. Berlin* **2**:1, 1891.

Marchand,⁴⁹ Grawitz⁵⁰). However, Ranvier,⁵⁰ in 1900, and Marchand⁵¹ in 1898 and 1902, traced the exudate cells back to peculiar elements which Ranvier called clasmatoocytes, and Marchand, adventitial cells.

I²³ have claimed since 1902 that the polyblasts have a double origin. They arise in part from local fixed cells, in part from non-granular blood leukocytes. The local cells in question are the resting wandering cells or the histiocytes (clasmatoocytes) in the common loose tissue and in the serous membranes. If inflammation starts in the lymphoid or myeloid tissue or in the spleen, it concerns the histiocytic reticular cells (Babkina⁵²). The same rôle is played in the liver by the cells of von Kupffer (Tschaschin⁵⁴). As it is best seen in vitally stained animals, these cells, under the influence of the inflammatory stimulus, wake up, mobilize, become active and are transformed into large, ameboid, phagocytic elements. The blood cells taking part in the formation of polyblasts are the lymphocytes and monocytes. They migrate out of the blood vessels, together with the special granular leukocytes. While the latter soon degenerate, the additional migration of nongranular cells into the tissue continues for a long period. The nongranular leukocytes undergo a rapid hypertrophy in the tissue; after two or three days, these hematogenous polyblasts cannot be distinguished from the polyblasts of histogenous origin.

This double origin of the polyblasts is natural, for a study of the embryonic histogenesis of the connective tissue and blood reveals a close relationship between the histiocytes and the nongranular leukocytes (Maximow⁵³ and Alfejew⁵⁴).

I have not been able to demonstrate the development of polyblasts from typical fibroblasts and from the endothelium of common blood vessels. New experiments recently undertaken in my laboratory with aseptic inflammation of various kinds in normergic and allergic animals, confirmed the results of my former experiments made to determine the origin of polyblasts.

Whereas the theory that the polyblasts, the inflammatory mononuclear exudate cells, develop through mobilization of resting wander-

49. Marchand, F.: Beteiligung der Leukocyten an der Gewebsneubildung, *Verhandl. d. X. Internat. Med. Cong. Berlin* 2:6, 1891.

50. Grawitz, P.: Beteiligung der Leukocyten an der Gewebsneubildung, *Verhandl. d. X. Internat. Med. Cong. Berlin*, 2:9, 1891.

51. Marchand, F.: Ueber Clasmatoocyten, Mastzellen und Phagozyten des Netzes, *Verhandl. d. deutsch path. Gesellsch.* 4:124, 1902; footnote 20.

52. Babkina, H.: Changes of the Tissue of the Blood Forming Organs in Aseptic Inflammation, *Inaug. Diss., St. Petersburg (Russian)*; abstr., *Folia Haemat.* 11:202, 1910.

53. Maximow, A.: Ueber die Entwicklung der Blut- und Bindegewebszellen beim Säugetierembryo, *Folia haemat.* 4:611, 1907.

54. Alfejew, S.: Die embryonale Histogenese der Zellformen des lockeren Bindegewebes der Säugetiere, *Folia haemat. Arch.* 30:111, 1924.

ing cells or histiocytes has met with general approval, the idea of the hematogenous origin of the major part of polyblasts did not become popular. Although a long series of investigators have confirmed my results (Ziegler,⁵⁵ Schwarz,⁵⁶ Helly,⁵⁷ Zieler,⁵⁸ Verebely,⁵⁹ Fischer,⁶⁰ Homén,⁶¹ von Fieandt,⁶² Wallgren,⁶³ Tschaschin,⁶⁴ Bergel,⁶⁵ Dantschakoff and Seidlein,⁶⁶ Kraft,⁶⁷ Stilwell,⁶⁸ Lang,⁶⁹ Alfejew⁷⁰), the vast

55. Ziegler, K.: Histologische Untersuchungen über das Oedem der Haut und des Unterhautzellgewebes, *Beitr. z. path. Anat. u. z. allg. Pathol.* **36**:435, 1904.

56. Schwarz, G.: Ueber die Herkunft der einkernigen Exsudatzellen bei Entzündungen, *Wien. klin. Wchnschr.* **17**:1173, 1904.

57. Helly, K.: Zur Morphologie der Exsudatzellen und zur Spezifität der weissen Blutkörperchen, *Beitr. z. path. Anat. u. z. allg. Pathol.* **37**:171, 1905.

58. Zieler, K.: Ueber die bei der aseptischen Entzündung des Bindegewebes auftretenden Zellformen, *Arch. f. Dermat. u. Syph.* **85**:323, 1907; Ueber Exsudatzellen bei der akuten aseptischen Entzündung des Bindegewebes, *Centralbl. f. allg. Pathol. u. path. Anat.* **18**:289, 1907.

59. Verebely, T. v.: Die Granulation des menschlichen Fettgewebes, *Beitr. z. klin. Chir.* **54**:320, 1907.

60. Fischer, O.: Ueber die Herkunft der Lymphozyten in den ersten Stadien der Entzündung. Experimentelle Studie, *Beitr. z. path. Anat. u. z. allg. Pathol.* **45**:400, 1909.

61. Homén, E.: Studien über experimentelle Tuberkulose in den peripheren Nerven und dem Bindegewebe bei gesunden und bei den alkoholisierten Tieren, *Arb. a. d. path. Inst. zu Helsingfors, series 1* **3**:91, 1911.

62. Fieandt, H. von: Beiträge zur Kenntnis der Pathogenese und Histologie der experimentellen Meningeal- und Gehirntuberkulose beim Hunde, *Arb. a. d. path. Inst. zu Helsingfors, series 1* **3**:235, 1911.

63. Wallgren, A.: Beitrag zur Kenntnis der Pathogenese und Histologie der experimentellen Lebertuberkulose, *Arb. a. d. path. Inst. zu Helsingfors, series 1*, **3**:139, 1911.

64. Tschaschin, S.: Ueber die Herkunft und Entstehungsweise der lymphozytoiden (leukozytoiden) Zellen, der "Polyblasten," bei der Entzündung, *Folia haemat. Arch.* **16**:247, 1913.

65. Bergel, S.: Beiträge zur Biologie der Lymphozyten, *Berl. klin. Wchnschr.* **56**:915, 1919; Beiträge zur Biologie der Lymphozyten, *Ztschr. f. exper. Path. u. Therap.* **21**:216, 1920; Weiteres zur lipoidspaltenden Funktion der Lymphozyten, *Beitr. z. path. Anat. u. z. allg. Pathol.* **73**:404, 1925.

66. Dantschakoff, W., and Seidlein, S.: Digestive Activity of Mesenchyme and Its Derivatives, *Biol. Bull.* **43**:97, 1922.

67. Kraft, I.: Ueber die entzündliche Neubildung von Bindegewebe bei den Knochenfischen, *Publications Inst. for Scientific Biol. Investigations, Univ. of Perm* **4**:25, 1925.

68. Stilwell, F.: On the Phagocytic Capacity of the Blood Vessel Endothelium of the Frog's Tongue and Its Presumed Transformation into Wandering Cells, *Folia haemat. Arch.* **33**:81, 1926.

69. Lang, F.: Rôle of Endothelium in the Production of Polyblasts (Mononuclear Wandering Cells) in Inflammation, *Arch. Path. and Lab. Med.* **1**:41, 1926.

70. Alfejew, S.: Beiträge zur vergleichenden Histologie des Blutes und des Bindegewebes. V. Ueber die entzündliche Histogenese des Bindegewebes beim Frosche (*Rana temporaria*), *Ztschr. f. mikr. anat. Forsch.* **9**:234, 1927.

majority of pathologists, especially in Germany and America, are skeptical about the progressive development of the nongranular leukocytes.

It is usually believed that the exudate cells develop from the "cells of the blood vessel wall" ("Gefässwandzellen" of the German authors). It is not always clear what is meant by this name. If it refers to the perivascular resting wandering cells (histiocytes), it is correct, although my experiments did not confirm an extensive proliferation of these elements, especially by the way of amitosis, as claimed by Marchand⁷¹ and others. In the majority of the papers, the endothelium itself is considered responsible for the production of polyblasts. It is supposed to be endowed with extraordinary cytopoietic activities and manifold potencies of development. Many authors consider these elements the most important factors in the defense reactions of the body. One of the manifestations of this ability is the presumed formation of exudate cells, of polyblasts in inflammation or of epithelioid cells in the tubercle.

Foot,⁷² using the method of intravenous injection of India ink, devised by McJunkin,⁷³ tried to follow the transformations of the endothelium in local and general reactive processes. The carbon particles are taken up not only by the littoral cells of the histiocytic system, but also to some extent, although irregularly, by the true endothelium of the peripheral blood vessels. If agar is introduced into the connective tissue or tuberculous inflammation produced in such an animal, the endothelial cells, labeled with carbon, according to Foot, become loose, isolate themselves and are transformed into ameboid polyblastic elements. Similar observations were made by Permar⁷⁴ on the endothelium of the vessels of the lung after introduction of a carmine sus-

71. Marchand, F.: Ueber den Entzündungsbegriff, *Virchows Arch. f. path. Anat.* **234**:245, 1921.

72. Foot, N.: Studies on Endothelial Reactions: I. The Macrophages of the Loose Connective Tissue, *J. M. Research* **40**:353, 1919; Studies on Endothelial Reactions: II. The Endothelial Cell in Experimental Tuberculosis, *J. Exper. Med.* **32**:513, 1920; Studies on Endothelial Reactions: III. The Endothelium in Experimental Pulmonary Tuberculosis, *J. Exper. Med.* **32**:533, 1920; Studies on Endothelial Reactions: IV. The Endothelium in Experimental General Miliary Tuberculosis in Rabbits, *J. Exper. Med.* **33**:271, 1921; Studies on Endothelial Reactions: V. The Endothelium in the Healing of Aseptic Wounds in the Omentum of Rabbits, *J. Exper. Med.* **34**:625, 1921; Studies on Endothelial Reactions: VI. The Endothelial Response in Experimental Tuberculous Meningoencephalitis, *J. Exper. Med.* **36**:607, 1922; Studies on Endothelial Reactions: VII. Changes in the Distribution of Colloidal Carbon Noted in the Lungs of Rabbits Following Splenectomy, *J. Exper. Med.* **37**:139, 1923; The Endothelial Phagocyte: A Critical Review, *Anat. Record* **30**:15, 1925.

73. McJunkin, F.: A Simple Technic for the Demonstration of Phagocytic Mononuclear Cells in Peripheral Blood, *Arch. Int. Med.* **21**:59 (Jan.) 1918.

74. Permar, H.: The Function of the Endothelial Cell in Pathological Conditions, Especially in Tuberculosis, *Am. Rev. Tuberc.* **9**:507, 1924.

pension into the respiratory passages and by Fritz Herzog⁷⁵ on the living endothelium of the capillaries of the frog's tongue. Marchand, who in his earlier papers⁷⁶ was of the opinion that the polyblasts in the inflamed omentum were derived from his "adventitial cells," i. e., the perivascular histiocytes, now,⁷⁷ with his student, Herzog,⁷⁸ believes that they originate from the vascular endothelium. He also traces the small lymphocytes, always found in inflamed areas, back to these endotheliogenous polyblasts and believes that they originate from the larger cells through amitosis. Herzog⁷⁹ has also described development of typical oxydase-positive granulocytes from the endothelium of blood vessels in the inflamed omentum and pia mater. In his latest paper,⁸⁰ he ascribes to this tissue an almost unlimited cytopoietic ability. The paper of Sabin, Doan and Cunningham⁸¹ may be quoted here; they believe that the "clasmatocytes" arise from endothelium. Finally, the sensational publications of Oeller⁸² and Töppich⁸⁷ should be mentioned. Oeller claims to have found a precipitous proliferation of the capillary endothelium in the lungs, with formation of round ameboid elements and, as has been already mentioned, even granulocytes in guinea-pigs which were sensitized against chicken erythrocytes and which had received an intravenous shock injection of this antigen. According to Töppich, similar phenomena occur after intratracheal application of tubercle bacilli in guinea-pigs.

In contradiction to these statements, I⁸² have always found that the true endothelial cells of the common blood vessels in adult mammals behaved as highly differentiated elements. They not only are unable to produce hemocytes, but they also have no ability to form even histiocytes and polyblasts. In early stages of embryogenesis they certainly possess the full mesenchymal potencies, which are gradually reduced in

75. Herzog, F.: Endothelien der Froschzunge als Phagozyten und Wanderzellen, *Ztschr. f. d. ges. exper. Med.* **43**:79, 1924; Ueber Beziehungen zwischen Dilatation, Durchlässigkeit und Phagozytose an den Capillaren der Froschzunge, *Virchows Arch. f. path. Anat.* **256**:1, 1925.

76. Marchand (footnote 20 and footnote 33, first reference).

77. Marchand, F.: Aeltere und neuere Beobachtungen zur Histologie des Omentum, *Haematologica* **5**:304, 1924; also footnote 33, second reference.

78. Herzog, G.: Experimentelle Untersuchungen über die Einheilung von Fremdkörpern, *Beitr. z. path. Anat. u. z. allg. Pathol.* **61**:377, 1916.

79. Herzog, G.: Zur Frage der Granulozytenbildung bei der Entzündung, *Centralbl. f. allg. Pathol. u. path. Anat.* **31**:481, 1921; Zellformen bei Meningo-encephalitis, *Centralbl. f. allg. Pathol. u. path. Anat.* **33**:228, 1922.

80. Herzog, G.: Ueber die Bedeutung der Gefäßwandzellen in der Pathologie, *Klin. Wchnschr.* **2**:684, 1923.

81. Sabin, F.; Doan, C., and Cunningham, R.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, *Contrib. Embryol.* **82**, Carnegie Inst., Washington **16**:125, 1925.

82. Maximow (footnote 23, first and sixth references).

later stages, and remain partially intact only in the littoral histiocytic elements of the liver, spleen, bone marrow, suprarenal and other organs.

In my studies on inflammation, I found that the true endothelium keeps its specific character and eventually forms new capillary sprouts. Similar conclusions have been reached by Clark and Clark⁸³ concerning the endothelium in the tail of living amphibian larvae. The same is true in tissue cultures. The only new developmental possibility open to the proliferating endothelial cells is that they may eventually recede from the vascular wall into the surrounding tissue and be transformed into fibroblasts. This can be observed in inflammation (Maximow²⁸) as well as in tissue cultures (Maximow⁸⁴). In living cultures of the leptomeninges, one can watch the outgrowth of endothelium from the severed ends of small arteries. It forms long bundles of parallel, slender, homogenous cells; they gradually move apart, form side processes and lose their differences from fibroblasts (Maximow⁸⁵). They are never seen to store vital dyes or to turn into ameboid elements. They are, however, able to ingest carbon particles passively when these particles come in contact with the protoplasm of the cells.

The observations of Foot and Herzog were tested by my students, Lang⁸⁶ and Stilwell,⁸⁸ and could not be confirmed. In local inflammatory reactions the carbon-marked endothelial cells of the small vessels were not seen to separate from each other and become ameboid. The carbon particles passed through the intact endothelium and were taken up by cells located outside the wall of the vessel, the pericytes. The latter eventually moved away from the vessels and were transformed into polyblasts. In contrast to the observations of Permar,⁷⁴ Lang⁸⁶ has shown in his studies on the behavior of lung tissue in vitro that the innumerable phagocytic cells typical for this tissue in vitro arise, not from capillary endothelium, but from peculiar histiocytes located

83. Clark, E. R., and Clark, E. L.: Reactions of Cells in the Tail of Amphibian Larvae to Injected Croton Oil (Aseptic Inflammation), *Am. J. Anat.* **27**:221, 1920.

84. Maximow, A.: The Cultivation of Connective Tissue of Adult Mammals in Vitro, *Arch. russes d'anat. d'histol. et d'embryol.* **1**:105, 1916; Untersuchungen über Blut und Bindegewebe. VII. Ueber "in vitro" Kulturen von lymphoidem Gewebe des erwachsenen Säugetierorganismus, *Arch. f. mikr. Anat.* **96**:494, 1922; Untersuchungen über Blut und Bindegewebe. VIII. Die zytologischen Eigenschaften der Fibroblasten, Retikulumzellen und Lymphozyten des lymphoiden Gewebes ausserhalb des Organismus, ihre genetischen Wechselbeziehungen und prospektiven Entwicklungspotenzen, *Arch. f. mikr. Anat.* **97**:283, 1923.

85. Maximow, A.: Ueber die Entwicklungsfähigkeiten der Blutleukozyten und des Blutgefässendothels bei Entzündung und in Gewebeskulturen, *Klin. Wchnschr.* **4**:1486, 1925.

86. Lang, F.: The Reaction of Lung Tissue to Tuberculous Infection in Vitro, *J. Infect. Dis.* **37**:430, 1925; Ueber Gewebeskulturen der Lunge, *Arch. f. exper. Zellforsch. besonders Gewebezüchtung (Explantation)* **2**:93, 1926.

in the septums between the alveoli. Aschoff,¹⁶ on the basis of the work of his student Seemann,⁴⁰ also doubts whether the capillary endothelium in the lung is able to phagocytose carbon particles. Lewis,⁸⁷ in his latest papers on aseptic inflammation, strictly denies the development of the macrophages from endothelium.

According to Töppich and Oeller,⁸⁸ whose observations on the endothelial origin of granular leukocytes in the allergic reaction of the lung have been mentioned, the first and most important manifestation of this reaction is an extremely rapid, mostly amitotic proliferation of the endothelium, resulting in the course of from fifteen to thirty minutes in the formation of round free cells, which later turn into granulocytes. From the standpoint of the general knowledge of the average speed of similar cellular transformations, these data sound highly improbable; in fact, they could not be confirmed by anybody (Seemann,⁴⁰ Gerlach and Finkeldey⁴¹ and others). They can be explained by the fact not taken into consideration either by Oeller or by Töppich, that the structure of the lungs in guinea-pigs and especially the accumulation of free cells in their tissue present great individual variations, even in animals in apparently normal condition (Seemann⁴⁰). Besides, the sudden accumulation of large quantities of free cells, whose intravascular or extravascular position in the lung cannot easily be made out, may be the result of local stagnation of white blood corpuscles in the lumen of the vessels.

Thus, the totality of the facts available makes the theory of the hemopoietic and histiocytopoietic ability of the common endothelium appear highly improbable. The endothelium belongs to the group of fibrocytes and is a relatively highly differentiated cell type. The controversies regarding the potencies of development ascribed to these elements by the various authors may be due partly to the indiscriminate use of the term "endothelium" when the littoral cells of the histiocytic system were meant. Thus, Domagk⁸⁸ and many others seem to believe that the cells lining the capillaries in the liver and spleen, on the one hand, and the endothelium of the lung capillaries, on the other, play an equally important rôle in the defense reactions by phagocytosing bacteria, disposing of foreign substances and producing free exudate cells.

The recent attempts of von Möllendorff²⁴ and his students, Koll²⁵ and Knake,²⁶ to explain the origin of granular leukocytes in an entirely

87. Lewis, W. H.: Macrophages of the Deep Fascia of the Thigh of the Rat in Spreads Supravitaly Stained with Neutral Red and with Janus Green, Tr. Am. A. Anatomists, 42d Session, New Haven, Anat. Record **32**:215, 1926. Macrophages in Sterile Inflammation of the Deep Fascia of the Rat, Am. A. Anatomists, 42d Session, New Haven, Anat. Record **32**:215, 1926.

88. Domagk, G.: Ueber das Auftreten von Endothelien im strömenden Blute nach Splenektomie, Virchows Arch. f. path. Anat. **249**:83, 1924.

new way, namely, from the "fibrocyte net," have been mentioned. They claim the same origin for the mononuclear exudate cells, i. e., for the polyblasts. They do not believe the resting wandering cells are separate, independent, well characterized cellular elements of the loose connective tissue. The histiocytes are merely a part of the diffuse "fibrocytic syncytium," cellular territories in a peculiar condition of metabolism. Under the action of an inflammatory stimulus, according to von Möllendorff, the whole net of fibrocytes breaks up into single cells. This process is accompanied by extremely rapid amitotic divisions. The free cells round off and appear as polyblasts. Whereas round, ameboid phagocytic cells storing electronegative vital dyes are generally supposed to be in an active condition, von Möllendorff believes that these qualities are a manifestation of a damaged condition of the cells. In later stages, when the local irritation subsides, the round cells again quickly turn back into fibrocytes. Von Möllendorff completely disregards the possibility of the hematogenous origin of at least a part of the polyblasts.

Although the conclusions of von Möllendorff are irreconcilable with the current opinion on the morphology of the local mesenchymal reactions, and although the adverse opinions are disregarded in his papers, his ideas have been accepted unqualifiedly by several writers in Germany. Thus, in a recent review "on the reticulo-endothelium and the active mesenchyme" written with much conviction, but without new confirming facts, Siegmund⁸⁹ accepts the whole of the von Möllendorff theory without reserve. He proclaims as a new and indisputable truth the conception that all connective tissue cells (fibrocytes) throughout the body are endowed with full embryonic properties, as in the embryo, and may be "activated" by suitable stimuli, especially parenterally introduced proteins. This far-reaching conclusion, which assumes that all connective tissue cells in the adult organism produce all kinds of blood cells indiscriminately and makes all morphologic distinction and classification of the connective tissue elements illusory, cannot be considered as a step forward in science. It is merely a return to the concept which prevailed in pathology in the nineties of the past century, when the histology of the connective tissue was in its infancy and all kinds of inflammatory elements were thought to be derived indiscriminately from "fixed connective tissue cells" (E. Ziegler,⁴⁸ Marchand,⁴⁹ Grawitz⁵⁰). The factual basis for this theory, as given by von Möllendorff and his school, is by no means flawless.

After the publication of von Möllendorff's papers, a series of controlling experiments was undertaken in my laboratory. They will serve

89. Siegmund, H.: Retikuloendothel und aktives Mesenchym, Beihefte z. Med. Klin. 23:1, 1927.

as material for a special paper. It is necessary to point out here only that, although the technic of von Möllendorff was used, sufficient proofs could not be found to corroborate his conclusions. After local injections of trypan blue solution, of India ink, of heterogenous serum or of formed antigens (foreign erythrocytes) in normergic and allergic animals, the same phenomena were revealed that I have previously described in various types of inflammation. Formation of polyblasts or granulocytes from fibrocytes was not encountered. It may be added that in the original slides of von Möllendorff, which are in my possession, the same pictures can be seen. Amitosis is not manifest, and the relations and development of the different types of cells are the same as in any other kind of inflammatory lesion.

It is highly regrettable that the investigations of von Möllendorff have wantonly stirred up again old controversies in a field which was always sufficiently confused and discredited because of its diversity of opinions and which only recently began to show symptoms of clarification.

The progressive development of the nongranular blood leukocytes, the lymphocytes and monocytes in inflammation after their migration from the blood vessels has been described by many authors. I laid special stress on these phenomena in all my papers. It is natural that a flawless experimental material and perfect histologic methods are necessary in order to obtain convincing microscopic pictures. It is probable that the vast majority of authors who flatly deny the possibility of the progressive development of lymphocytes have not had at their disposal material of the required quality. Marchand,⁹⁰ in his well known review of 1913, admits that it cannot be absolutely denied that some of the lymphocytes which migrated from the vessels can develop progressively in the tissue. Kiyono,¹⁵ although always trying to attribute the exclusive rôle in the production of polyblasts to the carmine-storing histiocytes, nevertheless is forced to admit that some of the lymphocytes also may develop into histiocytes or polyblasts. By doing this, he, of course, invalidates the basis of his theory.

It is clear that under such conditions new ways had to be found for a final test of the question under consideration. The method of tissue culture seemed to afford unusual opportunities in this respect. It is relatively easy to follow the transformations of the elements of the explanted tissue in the living condition as well as on fixed slides. The greatest difficulty for the discrimination of the cells of various origin in inflammatory lesions is the mixing from the earliest stages of local and hematogenous elements in the inflamed area. In tissue

90. Marchand, F.: Ueber die Herkunft der Lymphozyten und ihre Schicksale bei der Entzündung, *Verhandl. d. deutsch path. Gesellsch.* 16:5, 1913.

cultures it is possible to watch the transformations of both of these types of cells separately. The usual objection made against the observation *in vitro* is that the conditions here are abnormal and may not correspond to the processes occurring in the body. This is certainly true, but only so far as negative results obtained by the tissue culture method cannot necessarily exclude the possibility of a certain transformation in the organism. Positive cases, when cells of a certain type do show a series of changes and especially progressive development *in vitro*, prove beyond doubt that these cells are normally endowed with the respective potencies. If these changes are identical with the ones suggested by the observation in the organism, it would be illogical to deny the correctness of this interpretation.

With the final settlement of the problems of the morphology of inflammation as the chief goal, a series of experiments with explantation of various types of connective tissue were undertaken in my laboratory. It was found that the changes undergone by the various cells *in vitro* closely resemble the phenomena in inflammation.

When common loose connective tissue is explanted (Maximow⁹¹), the fibroblasts proliferate mitotically and migrate radially into the medium. They do not change their character and are never transformed into wandering cells. The endothelium either forms capillary sprouts or gives rise to additional fibroblasts. No granular leukocytes are ever seen to develop. On the contrary, large ameboid phagocytic mononuclear cells, polyblasts or macrophages are plentiful in the cultures. As there are no hematogenous cells available, they can originate in this case from only one source, through mobilization of the local histiocytes, the resting wandering cells.

When lymphoid (or myeloid) tissue is explanted (Maximow⁹²), the conditions are more complicated. But they again correspond exactly to what can be observed in inflammation of the lymphoid tissue in the body. Fibroblasts develop rapidly from the embryonic elements of the reticular syncytium. Large numbers of typical polyblasts or macrophages, mobilized reticular cells, arise from the same source. The lymphocytes in the tissue also give origin to similar polyblasts.

It is known that in specific inflammations, as in the formation of the tubercle in tuberculous lesions, the local defense reaction of the tissue displays certain typical modifications under the influence of the peculiar virus, as compared with the ordinary inflammatory process. The histogenesis of the tuberculous reaction, despite the enormous literature, is still under discussion, and here, as well as in ordinary inflammation, the rôle of the elements of the blood, the lymphocytes

91. Maximow (footnote 84, first reference).

92. Maximow (footnote 84, second and third references).

and the monocytes, in the formation of the tubercle, arouses sharp controversies. At present only a few pathologists attribute any rôle in the production of the epithelioid cells to the nongranular blood leukocytes.

The experiments with the cultures of lymphoid tissue, mentioned above, proved to be successful in elucidating the prospective potencies of the different cells. Therefore it was natural to apply this method for the explanation of the morphologic nature of the reaction of the tissue to tubercle bacilli (Maximow⁹³). The results have verified the expectations. Tubercle-like formations developed in vitro—clusters of large epithelioid cells and giant cells, phagocytosing bacilli and finally undergoing caseation. It could be easily made out that the source of the epithelioid cells, which are a peculiar type of polyblasts (Maximow²⁹), is double, as is the source of the polyblasts; some of them are mobilized reticular cells, i. e., local histiocytes; some are hypertrophied lymphocytes.

However, as in the lymphoid tissue there is a great variety of different cellular elements present, the transformation of the lymphocytes into polyblasts or epithelioid cells may not seem to some observers adequately proved, especially to those not sufficiently experienced in cytology. Thus, Shiomi,⁹⁴ who repeated my experiments with explantation of lymphoid tissue into blood plasma with various extracts, did not make a distinct histologic discrimination of the various cell types, and therefore his final conclusions are vague and indecisive.

It is evident that the solution of the problem receded further. It had to be sought in the cultivation of the cellular elements of the circulating blood. Whereas the cultures of common connective tissue have conclusively shown the transformation of the local histiocytes into polyblasts, the experiments with blood, in case of positive results, would settle the question of the ability of white blood corpuscles to produce polyblasts.

Awrorow and Timofejewsky⁹⁵ were the first to succeed in cultivating nongranular leukocytes of human leukemic blood in rabbit plasma. They found that they were transformed into polyblasts and even into fibroblast-like elements. They did not discriminate, however,

93. Maximow, A.: Tuberculosis of Mammalian Tissue in Vitro, *J. Infect. Dis.* **34**:549, 1924.

94. Shiomi, O.: Explantationsversuche mit Lymphknoten auf Plasma unter Zusatz von Milz-, Nebennieren- und Knochenmarkextrakt unter Nachprüfung der Versuche von Maximow und unter besonderer Berücksichtigung der Bildung granulierter Zellen, *Virchows Arch. f. path. Anat.* **257**:714, 1925.

95. Awrorow, P., and Timofejewsky, A.: Kultivierungsversuche von leukämischem Blute, *Virchows Arch. f. path. Anat.* **216**:184, 1914.

between lymphocytes and monocytes. Carrel and Ebeling⁹⁶ explanted the buffy coat of centrifugalized chicken blood and obtained what they believed to be "pure cultures of monocytes"; in their experiments, too, it was seen that the ameboid, proliferating elements were occasionally transformed into fibroblast-like cells. Fischer⁹⁷ confirmed the results of Carrel and Ebeling. He obtained in vitro cultures of ameboid phagocytic cells from the buffy coat of the blood of the chick and also termed them monocytes. He found that their transformation into fibroblast-like elements can be induced by adding to the culture fragments of dead muscle tissue.

It is obvious that, as these experiments were made with material from chickens, their conclusions cannot be directly applied to mammalian and human pathology. For my first experiments with cultures of leukocytes I⁹⁸ chose the rabbit, the animal I had used for the study of the histology of the inflammatory reaction. Special stress was laid on a distinct cytologic discrimination between the various types of cells. In explants of the buffy coat of the blood, put up with blood plasma and embryonic extract or extract from inflamed connective tissue, the white blood corpuscles undergo changes similar to those occurring in the inflamed area in the body after migration out of the blood vessels. The granular leukocytes of all kinds degenerate in the course of the first forty-eight hours. The lymphocytes and the monocytes, on the contrary, for the most part remain alive and show progressive development. The monocytes at once begin to hypertrophy, and in the first two or three days are transformed into large, ameboid, phagocytic elements, which in every respect correspond to the polyblasts or macrophages. Their protoplasm contains fat droplets, engulfed remnants of cells and erythrocytes. The transformations of the lymphocytes can be easily followed also in the living condition. A varying number of them, perhaps the youngest, die after one or two days; but most of them rapidly hypertrophy, and obtain an abundant, ameboid cytoplasm and kidney-shaped, clear, excentric nuclei. They join the monocytes in their further transformation into polyblasts. In such cultures gradual transitional forms also connect the lymphocytes with the hypertrophying monocytes as in an inflamed area. After four or five days all polyblasts in the culture are greatly enlarged. Outside the explant, in the fibrin, and in the interior of the explant, in the clefts between the dense masses

96. Carrel, A., and Ebeling, H.: Pure Cultures of Large Mononuclear Leucocytes, *J. Exper. Med.* **36**:365, 1922.

97. Fischer, A.: Sur la transformation, in vitro, des gros leucocytes mononucléaires en fibroblastes, *Compt. rend. Soc. de biol.* **92**:109, 1925.

98. Maximow, A.: Ueber die Entwicklungsfähigkeiten der Blutleukocyten und des Blutgefässendothels bei Entzündung und in Gewebeskulturen, *Klin. Wchnschr.* **4**:1486, 1925.

of blood platelets, small and large groups of huge, ameboid, sometimes epithelioid cells accumulate. They show mitotic proliferation. They contain a distinct cytocentrum with fat droplets and phagocytosed inclusions around it. If lithium carmine is added to the medium, they store large quantities of the dye in granular form. If small fragments of loose connective tissue are added to such cultures of leukocytes, the polyblasts infiltrate the tissue and produce pictures similar to those of inflamed connective tissue. Lewis,⁹⁹ in her experiments with incubated drops of blood from various animals and from man, came to similar conclusions regarding the formation of macrophages, epithelioid cells and giant cells from nongranular leukocytes.

In a special series of experiments, I¹⁰⁰ inoculated the cultures of leukocytes with tubercle bacilli. The lymphocytes as well as the monocytes attacked the colonies of tubercle bacilli and were transformed in the course of two or three days into large epithelioid cells, which surrounded the colonies in large clusters; the latter looked like tubercles. These experiments with the inoculation of cultures of leukocytes with tubercle bacilli have been repeated by Timofejewsky and Benewolenskaja.¹⁰¹ They fully confirmed the transformation of the lymphocytes and monocytes into epithelioid and giant cells.

Despite this seemingly conclusive evidence in favor of the possibility of a hematogenous origin of the common mononuclear exudate cells (i. e., the polyblasts and their special types, such as the tuberculous epithelioid cells) and of the developmental abilities of the lymphocytes and monocytes, the cardinal problem of the morphology of the local defense reaction still remained unsolved. In the abundant recent literature the rôle of the hematogenous elements is still almost completely disregarded. The idea that the polyblasts develop exclusively from the cells of the walls of the blood vessels (endothelium, adventitial cells, Herzog,¹⁰² Siegmund⁹⁸ and others) or from all local fixed elements of the connective tissue indiscriminately (von Möllendorff²⁴) is still dominant.

Even among the investigators using the tissue culture method, only Timofejewsky and Benewolenskaja¹⁰¹ and I¹⁰³ consider that the lymphocytes as well as the monocytes take part in the progressive

99. Lewis, M.: The Formation of Macrophages, Epithelioid Cells and Giant Cells from Leucocytes in Incubated Blood, *Am. J. Path.* **1**:91, 1925.

100. Maximow, A.: Rôle of the Nongranular Blood Leucocytes in the Formation of the Tubercle, *J. Infect. Dis.* **37**:418, 1925.

101. Timofejewsky, A., and Benewolenskaja, S.: Explantationsversuch von weissen Blutkörperchen mit Tuberkelbazillen, *Arch. f. exper. Zellforsch.* **2**:31, 1925.

102. Herzog (footnotes 78, 79 and 80).

103. Maximow (footnotes 98 and 100).

development which results in the production of polyblasts. The majority believes that the monocytes are genetically independent from the lymphocytes and that, whereas the developmental possibilities of the monocytes are admitted, the lymphocytes are incapable of progressive transformation (Hirschfeld¹⁰⁴). Lewis⁹⁹ doubts that lymphocytes change in vitro. Moreover, the development of regular connective tissue from leukocytes has not yet been observed; only "fibroblast-like" cells have been found.

The use of heparin (Craciun¹⁰⁵) enables investigators to apply tissue culture experiments to animals such as guinea-pigs and rats, which have been excluded from experimentation because their plasma clots rapidly. A new series of experiments with explantation of the buffy coat on a larger scale was therefore started in my¹⁰⁶ laboratory. The animals used were the chick, the rat, the guinea-pig and the monkey, *Macacus rhesus*. As in the work of Carrel and Ebeling⁹⁶ the morphologic side of the problem was not studied, and the true nature of the "monocytes in pure culture" remained doubtful, a careful histologic analysis of the transformations of the elements of the buffy coat in vitro with the supravital neutral red staining, sometimes combined with janus green (Simpson,³⁴ Sabin³⁵) was made. Results in all animals were similar in principle, but guinea-pigs seem to be especially favorable for culturing leukocytes.

The progressive changes of the lymphocytes in cultures of the buffy coat of the blood begin almost at once after explantation. Many of them remain unchanged and later gradually degenerate, but the major part is transformed in the course of from six to eight hours into typical polyblasts, large cells with an excentric kidney-shaped nucleus. In the blood the lymphocytes show few small neutral red vacuoles around the cytocentrum, while in vitro they rapidly develop a conspicuous roset of small and large neutral red vacuoles. The cells display intense ameboid movements, with formation of hyaline membrane-like pseudopodia. During the second day, the cells increase in size and accumulate fat droplets. In the meantime, the monocytes in the culture also hypertrophy and accumulate an increasing quantity of neutral red vacuoles and fat. After from two to three days, monocytes and lymphocytes indiscriminately have been transformed into typical large phago-

104. Hirschfeld, H.: Züchtungsversuche mit leukämischem Blut, *Folia haemat. Arch.* **34**:39, 1927.

105. Craciun, E.: Heparin-Plasma as Stock-Plasma for Tissue Cultures, *Bull. Johns Hopkins Hosp.* **38**:327, 1926.

106. Maximow, A.: Development of Nongranular Leucocytes (Lymphocytes and Monocytes) into Polyblasts (Macrophages) and Fibroblasts in Vitro, *Proc. Soc. Exper. Biol. & Med.* **24**:570, 1927.

cytic polyblasts. Thus, direct observation proves beyond doubt that lymphocytes develop rapidly into polyblasts (macrophages).

During the third day, many of the macrophages of lymphocytic and monocytic origin begin to stretch out and to develop long, spear-shaped, nonmotile processes, while the large nucleus acquires a more regular oval shape. After a period of a peculiar unstable equilibrium, during which intense stimuli, such as focusing under the microscope with powerful light, will cause the cells to contract rapidly and to reassume their ameboid condition, the polyblasts are finally (after six days or more) transformed irreversibly into typical fibroblasts. In cultures, grown in flasks, rather than on slides, these cells do not remain single. They proliferate mitotically and, joining each other, form large colonies of connective tissue which cannot be distinguished from cultures obtained from regular connective tissue. They consist of sheets of fibroblasts with scattered ameboid and quiescent histiocytes. Thus, the possibility of the transformation of a small lymphocyte into a macrophage (polyblast) and further into a fibroblast seems to be demonstrated.

The lymphocytes and the monocytes of the blood of the chick in vitro show similar transformations. Thus, the so-called "pure cultures of monocytes" of Carrel and Ebeling are in fact cultures of polyblasts (macrophages) which developed from lymphocytes and monocytes. It is not admissible to identify monocytes with polyblasts (macrophages). They are distinct morphologic conceptions. Haagen,¹⁰⁷ working under Fischer, recently came to similar conclusions.

Many lymphocytes of the chick in vitro were transformed into spindle-shaped elements, the thrombocytes.

The first crucial experiment for the demonstration of the polyblastic transformation of lymphocytes was recently made in my laboratory by Bloom.¹⁰⁸ As different types of leukocytes are present in the buffy coat of the blood, the objection could be made to the conclusions just mentioned that, since it is physically impossible to follow an individual cell in living condition in its transformations, monocytes, developing into polyblasts, might have been mistaken for lymphocytes. It is clear that to meet this criticism a material which contains nothing but lymphocytes should be explanted. The lymph of the thoracic duct of the rabbit is such a material. According to the dominant opinion

107. Haagen, E.: Die Bedeutung der Ionen im Kulturmedium für die explantierte Zelle, *Arch. f. exper. Zellforsch. bes. Gewebezüchtung (Explantation)* **3**:353, 1927.

108. Bloom, W.: Transformation of Lymphocytes of Thoracic Duct into Polyblasts (Macrophages) in Tissue Culture, *Proc. Soc. Exper. Biol. & Med.* **24**:567, 1927.

(Lejeune,¹⁰⁹ Thorne and Evans,¹¹⁰ Kindwall¹¹¹ and others), this liquid in mammals carries only insignificant quantities of, if any, other elements than small lymphocytes.

Bloom collected the lymph flowing from the thoracic duct of normal adult rabbits into small tubes and allowed it to clot. The clots were then minced into small fragments and explanted in the usual way into blood plasma to which various extracts had been added. The result was always uniform and conclusive. The lymphocytes changed with extreme rapidity—in the course of a few hours—into larger cells which were gradually, in three days and more, transformed into typical large ameboid, carmine-storing polyblasts. After five days, these cells gave rise to typical large, flat, nonmotile fibroblasts with spear-shaped processes.

Thus, the possibility of the transformation of a small lymphocyte into a polyblast (macrophage) and finally into a fibroblast, a common fixed connective tissue cell, as advanced in my²⁹ first publication on inflammation and agreed to by French authors, among others (Renaut,³ Dubreuil¹¹²), has found its final experimental confirmation.

This process of progressive development and differentiation plays an important rôle in all types of local defense reactions. It need not be considered the only type of reaction, as Renaut,³ for instance, believed. The mobilization of local elements is the other, no less important, method of response of the organism to the local action of an irritating or injurious factor.

HISTOLOGY OF ALLERGIC INFLAMMATORY REACTION

It is known that the organism, through repeated parenteral introductions of a foreign protein, is sensitized to that specific substance. The connective tissue in a sensitized animal reacts in a peculiarly rapid and intense way to a renewed local introduction of the antigen. A classic example of this "allergic inflammation" is the so-called "phenomenon of Arthus," that is, the reaction of the subcutaneous tissue of

109. Lejeune, E.: Die Zellen im Ductus lymphaticus beim Menschen und einigen Säugern, unter spezieller Berücksichtigung der "grossen Mononukleären," *Folia haemat. Arch.* **19**:371, 1915.

110. Thorne, G., and Evans, H.: Absence of Monocytes in Thoracic Duct Lymph, *Anat. Record* **23**:42, 1922.

111. Kindwall, J.: A Supravital Study of the Cells in the Lymph Stream of the Rabbit, *Bull. Johns Hopkins Hosp.* **41**:39, 1927.

112. Dubreuil, G.: Le chondriome et le dispositif de l'activité sécrétoire aux différents stades du développement des éléments cellulaires de la lignée connective, descendants du lymphocyte (Globules blancs mononucléés de la lymphe et du sang, cellules connectives, cartilagineuses et osseuses), *Arch. d'anat. micr.* **15**:53, 1913.

the rabbit, sensitized to horse serum, to a further subcutaneous injection of this antigen.

The special histogenesis of the modified inflammatory reaction has been the subject of several experimental investigations, especially by Rössle¹¹³ and by Gerlach.⁹

As far as one can judge by the still modest accumulation of facts available at present, the differences, as compared with the histogenesis of common inflammation, are quantitative rather than qualitative. The obstruction of the blood vessels of the affected area, the damaging of their walls and an intense edema are the salient features. Increased degeneration of the fixed cells, on one hand, and increased migration of special and eosinophilic leukocytes and of lymphocytes, on the other, have been observed. Detailed study of the histology of the allergic reactions is still needed.

GENERAL DEFENSE REACTIONS

When soluble or finely dispersed foreign or toxic substances or micro-organisms find their way into the organism and are distributed over the whole body or at least over large sections of it, the organism answers with a general reaction which manifests itself, among other phenomena, by the "activation" of the "mesenchyme," i. e., connective tissue and blood, in various places of the body (Siegmund,²² von Gaza¹¹⁴ and others). The reaction may present differences in detail according to the nature of the injurious agent, but in principle the response of the organism is always the same.

Speaking generally, three cellular systems are believed to play an important rôle in this reaction: (1) two kinds of hemocytes—the granular leukocytes and the monocytes, (2) the true endothelium of the common blood vessels and (3) the system of the histiocytes (reticulo-endothelium). All these elements seem to manifest their activity in the tissues outside the vessels and in the interior of the vascular channels as well.

A Hemocytes.—Leukocytosis: It is well known that in most infections the number of the special polymorphonuclear leukocytes (in man the neutrophils) is increased in the circulating blood—so-called leukocytosis. This phenomenon is supposed to be the visible manifestation of the increased activity of these elements. In most cases the increased outpouring of mature cells into the circulation is accom-

113. Rössle, R.: Ueber die Merkmale der Entzündung im allergischen Organismus, Verhandl. d. deutsch path. Gesellsch. 17:281, 1914.

114. Gaza, W. von: Die Aktivierung des Mesenchyms. Zugleich ein Beitrag zur örtlichen Vitalfärbung maligner Tumoren am Menschen, Klin. Wchnschr. 4:745, 1925.

panied by their increased formation in the bone marrow. This is a vital reaction of the bone marrow to the action of toxins. Types of leukocytes, younger than usual, and sometimes even myelocytes may appear in the blood. In cases in which the toxic products of the micro-organisms have a direct deleterious effect on the special granulocytes, as in typhoid fever, leukopenia occurs, and instead of neoformation of these elements in the bone marrow, visible signs of a decrease in the quantity of myelocytes can be found. Severe lesions of the system of the special granulocytes are known to reduce the resistance of the organism toward infections (agranulocytic angina).

The increase in number of the special leukocytes in infections is perhaps not so much a reaction aiming directly at the pathogenic micro-organisms, as a manifestation of an increase of a resorptive function, which disposes of the products of the decomposition of foreign proteins. It is known also that leukocytosis and increased production of special leukocytes after a short period of leukopenia follow the parenteral introduction of foreign proteins, as has been shown in different experiments with the so-called nonspecific protein therapy (Petersen¹¹⁵).

General eosinophilia is manifested by an increased formation of eosinophils in the bone marrow and an increase of the number of these cells in the blood. It often, but not necessarily, accompanies the local eosinophilic reactions (in bronchial asthma, echinococcus infection and similar conditions). The eosinophils of general eosinophilia are common eosinophilic leukocytes and, as a rule, originate exclusively in the bone marrow.

Schlecht,¹¹⁶ Schlecht and Schwenker¹¹⁷ and others have shown that after parenteral introduction of different proteins or their derivatives in sensitized animals, general eosinophilia may ensue. It should therefore be considered a reaction to toxic products overflowing the organism, arising in the body, as the result of disintegration of foreign or abnormal endogenous proteins.

Extramedullary Myelopoiesis: In many cases of an abnormally increased and intensified general granulocytic reaction of the organism, which occurs in various infections or intoxications, myeloid elements, especially young forms of granulocytes (myelocytes), appear in the

115. Petersen, W.: *Protein Therapy and Nonspecific Resistance*, New York, The Macmillan Company, 1922.

116. Schlecht, H.: Ueber experimentelle Eosinophilie nach parenteraler Zufuhr artfremden Eiweisses und über Beziehungen der Eosinophilie zur Anaphylaxis, *Arch. f. exper. Path. u. Pharmacol.* **67**:137, 1912.

117. Schlecht, H., and Schwenker, G.: Ueber die Beziehungen der Eosinophilie zur Anaphylaxie, *Deutsches Arch. f. klin. Med.* **108**:405, 1912.

adult body in places in which they are not found under physiologic conditions. This phenomenon, the so-called myeloid metaplasia or extramedullary myelopoiesis, is not considered a compensatory regeneration due to the insufficiency of the bone marrow. It is a reaction of the local tissue or of the blood in certain areas of the circulatory system to abnormal stimuli connected with the accumulation in the organism of foreign substances, perhaps products of protein decomposition or bacterial toxins, which are neutralized, transformed and resorbed. Sometimes local extramedullary myelopoiesis can be observed, confined to a limited place in the body, when the general condition of the organism seems to be normal. An example is the formation of bone marrow which occurs in the wall of the pelvis of the kidney of the rabbit after ligation of the blood vessels of the kidney (Sacerdotti and Frattin¹¹⁸), Poscharissky,¹¹⁹ Maximow¹²⁰).

The morphologic study of extramedullary myelopoiesis, especially in experimental conditions, is important, because when myeloid elements arise in an unusual place in the body, their origin and their genetic relationships to the lymphoid elements and other tissue cells can be easily elucidated.

In the modern literature on pathology, local fixed elements, "cells of the blood vessel wall" or "endothelial cells" are usually said to be responsible for the production of myeloid tissue (Schridde,¹²¹ Fischer,¹²² Herzog,¹²³ Damberg,¹²⁴ Schaak,¹²⁵ Dieckmann,¹²⁶ Herzenberg,¹²⁷

118. Sacerdotti, C. and Frattin, G.: Ueber die heteroplastische Knochenbildung. Experimentelle Untersuchungen, Virchows Arch. f. path. Anat. **168**:431, 1902.

119. Poscharissky, J.: Ueber heteroplastische Knochenbildung. Eine pathologisch-histologische und experimentelle Untersuchung, Beitr. z. path. Anat. u. z. allg. Pathol. **38**:135, 1905.

120. Maximow, A.: Experimentelle Untersuchungen zur postfötalen Histogenese des myeloiden Gewebes, Beitr. z. path. Anat. u. z. allg. Pathol. **41**:122, 1907.

121. Schridde, H.: Ueber die Histogenese der myeloischen Leukämie, München. med. Wchnschr. **55**:1057, 1908.

122. Fischer, H.: Die myeloische Metaplasie und fötale Blutbildung und deren Histogenese, Berlin, Julius Springer, 1909.

123. Herzog (footnotes 78 and 79).

124. Damberg, S.: Ueber die extramedulläre Bildung des hämatopoetischen Gewebes, Folia haemat. Arch. **16**:210, 1913.

125. Schaak, W.: Die Veränderungen des Blutes und der blutbildenden Organe nach Amputation und Exartikulationen, Folia haemat. Arch. **15**:394, 1913.

126. Dieckmann, H.: Histologische und experimentelle Untersuchungen über extramedulläre Blutbildung, Virchows Arch. f. path. Anat. **239**:451, 1922.

127. Herzenberg, H.: Zur Frage der extramedullären Granulo- und Erythropoese, Beitr. z. path. Anat. u. z. allg. Path. **73**:55, 1924.

Nägeli,¹²⁸ Oeller,⁹⁶ Mandelstamm,¹²⁹ Brack,¹³⁰ Ssyssojew¹³¹ and others). Many authors do not seem to differentiate between the true endothelium of common blood vessels and the littoral histiocytes which line the sinusoids in the spleen, liver and suprarenals. Thus, Siegmund⁸⁸ describes development of myelocytes from Kupffer cells in the liver after intravenous injections of living colon bacilli.

According to Dominici,¹³² the myeloid elements in the experimental myeloid metaplasia of the spleen and in the lymph nodes develop from local lymphocytes. A similar point of view is taken by Babkina,⁵² Selling,¹³³ Downey and Weidenreich,¹³⁴ Weill,¹³⁵ Firket and Campos,¹³⁶ Jordan and Marshall,¹³⁷ Jolly¹³⁸ and others. Studying the formation of bone marrow in the kidney of the rabbit after vasoligation, I¹²⁰ found that in this tissue, which does not possess any local lymphocytes, the first myeloid cells appear intravascularly in the enlarged lumen of capillaries filled with stagnating blood. The lymphocytes of this blood hypertrophy and are transformed into hemocytoblasts, which in their turn differentiate into erythroblasts, myelocytes and megacaryocytes. Thus, this process may be considered a kind of colonization of the tissue with hemopoietic stem cells. This observation agrees with the unitarian theory of hemopoiesis, which does not recognize any difference between

128. Nægeli, O.: *Blutkrankheiten und Blutdiagnostik*, ed. 4, Berlin, Julius Springer, 1923.

129. Mandelstamm, M.: Ein Beitrag zur Frage der Hämo-poesie im Nierenbecken, *Virchows Arch. f. path. Anat.* **253**:587, 1924.

130. Brack, E.: Anatomische Studie über die leukopoetischen Systemerkrankungen (ausschliesslich der Myelome), *Virchows Arch. f. path. Anat.* **248**:357, 1924.

131. Ssyssojew, T.: Experimentelle Untersuchungen über die Blutbildung in den Nebennieren, *Virchows Arch. f. path. Anat.* **250**:291, 1926.

132. Dominici, H.: Histologie de la rate au cours des états infectieux, *Arch. de méd. expér. et d'anat. path.* **12**:733, 1900; Sur l'histologie de la rate à l'état normal et pathologique, *Arch. d. méd. expér. et d'anat. path. (series 1)* **13**:1, 1901; Sur le plan de structure du système hématopoiétique des mammifères, *Arch. d. méd. expér. et d'anat. path. (series 1)* **13**:473, 1901.

133. Selling, L.: Benzol als Leukotoxin. Studien über die Degeneration und Regeneration des Blutes und der hämatopoetischen Organe, *Beitr. z. path. Anat. u. z. allg. Pathol.* **51**:576, 1911.

134. Downey, H., and Weidenreich, F.: Ueber die Bildung der Lymphocyten in Lymphdrüsen und Milz. IX. Fortsetzung der "Studien über das Blut und die blutbildenden und zerstörenden Organe," *Arch. f. mikr. Anat.* **80**:306, 1912.

135. Weill, P.: Ueber die Bildung von granulierten Leukozyten im Karzinomgewebe, *Virchows Arch. f. path. Anat.* **226**:212, 1919.

136. Firket, J., and Campos, E.: Generalized Megalocaryocytic Reactions to Saponin Poisoning, *Bull. Johns Hopkins Hosp.* **33**:271, 1922.

137. Jordan, H., and Marshall, H.: Metaplastic Development of Erythrocytes in Lymph Nodes, *Anat. Record* **29**:363, 1925.

138. Jolly, J.: *Traité technique d'hématologie*, Paris, A. Maloine et fils, 1923.

the potentialities of the lymphocytes and the myeloid stem cells and claims that the lymphocytes under suitable external conditions may produce all kinds of blood cells.

The recent paper of Lang,¹³⁹ who studied experimental extramedullary myelopoiesis in rabbits intravitaly stained with carmine and injected with blood poisons (phenylhydrazin, sapotoxin), with *B. coli* vaccine or with living colon bacilli, shows that myeloid elements outside the bone marrow may be formed in two ways; thus he reconciles the two opposite views. On the one hand, large basophilic hemocytoblasts appear in the lumen of the capillary veins in various organs. They obviously develop through hypertrophy from the common small lymphocytes—a phenomenon corresponding to my¹²⁰ previous observations in the kidney and to those of Wallgren¹⁴⁰ in the liver. These intravascular hemocytoblasts produce erythroblasts, myelocytes and megacaryocytes through mitosis and differentiation. In later stages the myeloid elements in the liver, the spleen and the suprarenal pass into the tissue. This is not true emigration, however, but merely passive penetration through the thin syncytial histiocytic wall of the vessel.

On the other hand, in the lymph nodes, where myelocytes usually also develop from local lymphocytes, in cases with intense and rapid production of myelocytes, the latter arise directly from fixed undifferentiated embryonic cells accompanying the blood capillaries; the stage of the large free basophilic hemocytoblasts is skipped. It is interesting that this happens especially in germ centers, where, according to the dualistic theory, myeloid metaplasia is not possible (Nägeli¹²⁸). Another proof in favor of the unitarian conception of the myeloid potency of the lymphocyte has recently been given by Bloom.¹⁴¹ He showed that in the germ centers of the malpighian nodules of the spleen and of the primary nodules in the lymph nodes in allergic guinea-pigs small lymphocytes are transformed directly into special micromyelocytes. This confirms the old descriptions given by Dominici.¹³²

Thus, myeloid elements in extramedullary myelopoiesis can develop both from local fixed embryonic cells (especially in lymph nodes) and from free, local or hematogenous embryonic elements, the lymphocytes.

B. Endothelium.—The endothelium, which lines the wall of the whole circulatory system and is the mediator between the blood and the tissues, is, as a rule, the first cell type to come in contact with the foreign factors affecting the organism as a whole. If sterile particulate matter,

139. Lang, F.: Experimentelle Untersuchungen über die Histogenese der extramedullären Myelopoese, *Ztschr. f. mikr. anat. Forsch.* **4**:417, 1926.

140. Wallgren, A.: Zur Kenntnis der lymphoiden Zellen des Kaninchenblutes, *Folia haemat.* **8**:307, 1909.

141. Bloom, W.: Hemopoietic Potency of the Small Lymphocyte, *Folia haemat. Arch.* **33**:122, 1926.

such as India ink, finds its way into the blood, the major part of it is at once taken up by the histiocytes of certain organs. A fair portion, however, is deposited on the surface of the common endothelial cells all over the circulatory system, with a seemingly irregular and indefinite distribution (McJunkin,⁷³ Foot,⁷² Lang,⁶⁹ Stilwell⁶⁸ and others). The particles soon enter the protoplasm of the endothelial cells, which do not show any appreciable changes. Shortly afterward they pass through the endothelium into the surrounding tissue, where they are taken up by pericytes and histiocytes (Lang⁶⁹ and Stilwell⁶⁸). If living micro-organisms enter the blood, they seem to be phagocytosed mainly by the littoral elements of the histiocytic system. Some exceptions, however, may exist. Thus, according to Hammerschmidt,¹⁴² if bacilli isolated from the brain of dogs infected with rabies are injected intravenously into mice, for which the micro-organisms are highly pathogenic, they are electively taken up by the endothelium of the smaller vessels all over the body.

Numerous observers insist that the common endothelium participates actively in the general defense reaction against intravascular obnoxious agents. Countless indications of a "swelling" and "rounding up" of endothelium caused by toxins can be found in infectious diseases, as again recently emphasized by Davydowskie¹⁴³ for spotted typhus. The swollen endothelial cells are supposed to round off and become free in the lumen of the vessels. According to a widely spread conception this is the method of formation of monocytes in endocarditis lenta and in other pathologic conditions accompanied by monocytosis (Bittorf,¹⁴⁴ Hess¹⁴⁵ and others).

Convincing microscopic proofs for this idea have never been given. As has been pointed out, the cytopoietic potencies of the common endothelium are small, and the only transformation which can be easily demonstrated is the production of fibroblasts.

I have mentioned that the sensational data of Oeller,³⁶ Töppich⁸⁷ and others concerning an intense cytopoietic reaction of the endothelium of the capillaries of the lung in response to the injection of antigen in sensitized animals have not been confirmed. Fried¹⁴⁶ also failed to

142. Hammerschmidt, J.: Die Rolle der Endothelzellen bei septischen Infektionen, *Klin. Wchnschr.* **6**:651, 1927.

143. Davydowskie, J.: Die pathologische Anatomie und Pathologie des Fleckfiebers, *Ergebn. d. allg. Pathol. u. path. Anat.* **20**:571, 1924.

144. Bittorf, A.: Endothelien im strömenden Blute und ihre Beziehungen zu hämorrhagischer Diathese, *Deutsches Arch. f. klin. Med.* **133**:64, 1920.

145. Hess, F.: Zur Herkunft der im strömenden Blut bei Endocarditis lenta vorkommenden Endothelien, *Deutsches Arch. f. klin. Med.* **138**:330, 1922.

146. Fried, B.: The Origin of Histiocytes (Macrophages) in the Lungs. An Experimental Study by the Use of Intratracheal Injections of Vital Stain, *Arch. Path. & Lab. Med.* **3**:751 (May) 1927.

find any indication of a cytopoietic activity of the endothelium of the vessels of the lung.

The rôle of the endothelium in the adsorption and neutralization of toxins and in other general reactions combating infections or intoxications may be important; but it is not manifest in appreciable morphologic changes.

C. *Histiocytes*.—Of all the cell systems instrumental in general defense reactions, the histiocytic apparatus is doubtless the most important (Aschoff¹⁴⁶ and Schittenhelm¹⁴⁷). The location and distribution of its elements seems to be well adapted to this function. The histiocytes are scattered in the connective tissue over the whole body, accumulating in some places, as in the blood-forming organs, in large masses. Besides, as "littoral cells," they line certain areas of the blood and lymph vascular system.

It is well known that the histiocytes play a leading rôle in the intermediate metabolism of various substances, for instance, fat and lipoids (Anitschkow,¹⁴⁸ Zinserling,¹⁴⁹ Schönheimer¹⁵⁰), hemoglobin and iron. They are supposed to take part in the production of bile pigment.

The reaction of histiocytes to foreign colloidal substances introduced parenterally into the general circulation is best illustrated by their behavior in vital staining of the organism with electronegative acid aniline dyes (pyrrhol blue, isamine blue, trypan blue), with lithium carmine or with colloidal metals, as collargol (Goldmann,¹³ Tschaschin,¹⁴ Kiyono¹⁵).

The histiocytes store the vital dye in granular form. The colloidal particles are supposed to enter the protoplasm invisibly through "ultra-microscopic phagocytosis" and to become gradually condensed in the body of the cell. When the agglomerations of the colloidal particles reach a sufficient size, they become microscopically visible and appear as granules. The latter increase in size through addition of new particles until an equilibrium is established between the inner and the outer medium. According to the quantity of histiocytes present, a tissue or an

147. Schittenhelm, A.: Normale und pathologische Physiologie des retikulo-endothelialen Systems, Handbuch der Krankheiten des Blutes und der blutbildenden Organe, edited by A. Schittenhelm, Berlin, Julius Springer, 1925, vol. 2, p. 492.

148. Anitschkow, N.: Ueber experimentell erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Beitr. z. path. Anat. u. z. allg. Pathol. **57**:201, 1914; Experimentelle Untersuchungen über die Ablagerung von Cholesterinfetten im subkutanen Bindegewebe, Arch. f. Dermat. u. Syph. **120**:627, 1914.

149. Zinserling, W.: Ueber die Anfangsstadien der experimentellen Cholesterinverfettung, Beitr. z. path. Anat. u. z. allg. Pathol. **71**:292, 1923.

150. Schönheimer, R.: Ueber die experimentelle Cholesterinkrankheit der Kaninchen, Virchows Arch. f. path. Anat. **249**:1, 1924.

organ shows more or less marked macroscopic color. The spleen, liver, lymph nodes and bone marrow usually show the deepest staining. Of course, the distribution of the dye in the various groups of histiocytes in the body depends on the grade of dispersion of the solution, on the way and method of introduction of the dye and on its accessibility to the respective histiocytes. In all cases of vital staining, the ability of the cells to store colloidal dyes is closely connected with their ability to mobilize, to change into free ameboid cells, giant cells and epithelioid cells and to phagocytose. Amebism is typical for all histiocytes; it manifests itself, however, only under the influence of certain stimuli. The extensive locomotion of the histiocytes in the body, claimed by Goldmann, has not been confirmed (Kuczynski¹⁵¹), and the seemingly extreme changes in the distribution of these cells have been more adequately explained by the great changes of the storing ability under the influence of various stimuli. At any rate, the motility of the histiocytes remains an important factor in the resorption and secretion of various substances (Kiyono and Nakanoin¹⁵²).

Exogenous or endogenous particulate matter circulating in the blood, such as particles of intravenously injected India ink, dead erythrocytes or leukocytes and other substances, are rapidly disposed of through the activity of the histiocytic apparatus. They are engulfed especially by the histiocytic littoral cells of the liver, the spleen, the bone marrow and the lymph nodes. The extravascular histiocytes also accumulate foreign particles, but to a much smaller extent, which is generally regulated by the size of the particles of the colloidal solution and their accessibility to the cells. Thus, the reticular histiocytes of the red pulp of the spleen or the myeloid tissue, where the walls of the sinusoids are highly permeable, receive a fair amount of injected India ink, whereas the extravascular histiocytes in the common connective tissue often have no chance to obtain even a small amount of the foreign substance.

The histiocytes which have stored a certain substance may have a different fate. If the substances or the particles are digestible, they are gradually dissolved by the protoplasm and disappear. They may first undergo visible changes; thus during intracellular digestion, carmine granules acquire a yellowish or black color. The soluble products are excreted by the organism, and the histiocytes may gradually assume their former structure. In some cases the stored substance is believed to be transferred to other cells; thus, carmine, according to Schittenhelm

151. Kuczynski, M.: Edwin Goldmanns Untersuchungen über celluläre Vorgänge im Gefolge des Verdauungsprozesses auf Grund nachgelassener Präparate dargestellt und durch neue Versuche ergänzt, *Virchows Arch. f. path. Anat.* **238**:185, 1922.

152. Kiyono, K., and Nakanoin, T.: Weitere Untersuchungen über die histiozytären Zellen, *Acta scholae medicinalis Universitatis Imperialis in Kioto* **3**:55, 1919.

and Erhardt,¹⁵³ passes from the Kupffer cells into the liver cells. In cases in which the histiocytes store excessive amounts of an indifferent substance or in which the substance itself proves to be toxic (colloidal silica, Gye and Purdy¹⁵⁴), the cells may undergo degeneration. The stored substances which are freed by the disintegrating cells may be taken up by other histiocytes.

If the histiocytes are filled with indigestible substances, such as metallic silver (collargol) or carbon particles, the process of "self-purification" of the histiocytic system is slow and proceeds in complicated ways (Kiyono¹⁵ and Aschoff¹⁶). The particles are partly set free through the disintegration of the phagocytes, or they retain an intracellular position and in both cases are transported with the lymph or the blood to new places in the body. Finally, they may leave the organism through the lungs in the form of so-called "dust cells" (Lang¹⁵⁵). According to Petroff,¹⁵⁶ the collargol stored by histiocytes may be gradually eliminated through the intestine.

In cases in which saprophytic or pathogenic micro-organisms are circulating in the blood, the reaction of the histiocytes can be compared to their behavior toward aseptic particulate matter. This has been well known since the fundamental work of Wyssokowitsch,¹⁵⁷ whose results have been confirmed by a long series of subsequent workers. Among the latest contributors, Domagk¹⁵⁸ and Siegmund⁸⁸ may be mentioned. The micro-organisms are rapidly phagocytosed by the littoral histiocytes in the liver, spleen and bone marrow. In the case of pathogenic micro-organisms, the outcome of the infection largely depends on the extent and efficiency of this phagocytic reaction.

The morphologic changes of the histiocytes in such cases also correspond in principle to those mentioned for the foreign colloidal and particulate substances. Under the influence of the functional stimulation, the histiocytes enlarge, swell, bulge into the lumen of the sinusoids

153. Schittenhelm, A., and Erhardt, W.: Untersuchungen über die Beziehungen des reticulo-endothelialen Systems zu den grossen Monozyten des Blutes mit Hilfe der Vitalspeicherung, *Ztschr. f. d. ges. exper. Med.* **46**:225, 1925.

154. Gye, W., and Purdy, W.: The Poisonous Properties of Colloidal Silica. III. *Brit. J. Exper. Path.* **5**:238, 1924.

155. Lang (footnote 86, second reference).

156. Petroff, I.: Zur Frage nach der Speicherung des kolloidalen Silbers im retikuloendothelialen System, *Ztschr. f. d. ges. exper. Med.* **42**:242, 1924.

157. Wyssokowitsch, W.: Ueber die Schicksale der ins Blut injizierten Mikroorganismen im Körper der Warmblüter, *Ztschr. f. Hyg. u. Infektionskrankh.* **1**:1, 1886.

158. Domagk, G.: Untersuchungen über die Bedeutung des retikuloendothelialen Systems für die Vernichtung von Infektionserregern und für die Entstehung des Amyloids, *Virchows Arch. f. path. Anat.* **253**:594, 1924.

and increase in numbers. They may show mitotic proliferation and isolate themselves in the form of free cells. The digestive activity toward the micro-organisms manifests itself usually in vacuolization of the cells and in progressive degenerative changes of the engulfed micro-organisms, accompanied by loss of staining ability and other changes.

In specific infections, such as tuberculosis or leprosy, the phagocytic side of the defense reaction of the histiocytes is most prominent. As has been explained, the essential constituents of the tubercle, the epithelioid and giant cells, develop from histiocytes. Lepa cells are also to a large extent modified histiocytes (Oliver¹⁵⁹). An additional source of these polyblasts (inflammatory macrophages), varying in its extent according to the local circumstances, is furnished, as has been seen, by the lymphocytes and monocytes.

The phenomena can be easily reproduced outside the body in tissue cultures (Maximow¹⁶⁰).

The phagocytosis of tubercle and lepra bacilli by histiocytes may not always have a favorable outcome for the organism. The micro-organisms may eventually multiply in the interior of living cells; in this case the latter may be instrumental in the further dissemination of the infection (Cunningham, Sabin, Sugiyama and Kindwall¹⁶¹). The tissue culture method gives good opportunities for studying these peculiar symbiotic interrelations between living cells and micro-organisms.

A much vaster domain than the visible manifestations of the defensive function of the histiocytes, as phagocytosis, is the problem of their humoral immunization activity—production of enzymes, participation in the formation of antibodies and hemolysins and other functions. An increasing amount of information is accumulating on this subject (Aschoff¹⁶ and Schittenhelm¹⁴).

One of the important questions pertaining to the activity of the histiocytes as producers of various internal secretions is the problem of their so-called blockade. It has been observed that histiocytes, after having stored a sufficient amount of a certain substance, become less efficient or totally incapable of performing certain other functions, for instance, elaboration of antibodies or bile pigment (Lepehne,¹⁶² Nis-

159. Oliver, J.: The Origin of the Lepa Cells, *J. Exper. Med.* **43**:233, 1926.

160. Maximow (footnotes 93 and 100).

161. Cunningham, R.; Sabin, F.; Sugiyama, S., and Kindwall, J.: Rôle of the Monocyte in Tuberculosis, *Bull. Johns Hopkins Hosp.* **37**:231, 1925.

162. Lepehne, G.: Milz und Leber. Ein Beitrag zur Frage des hämatogenen Ikterus, zum Hämoglobin- und Eisenstoffwechsel, *Beitr. z. path. Anat. u. z. allg. Pathol.* **64**:55, 1918; Zerfall der roten Blutkörperchen beim Ikterus infectiosus (Weil). Ein weiterer Beitrag zur Frage des hämatogenen Ikterus, des Hämoglobin- und Eisenstoffwechsels, *Beitr. z. path. Anat. u. z. allg. Pathol.* **65**:163, 1919.

sen,¹⁶³ Bieling and Isaac,¹⁶⁴ Gay and Clark,¹⁶⁵ Elek,¹⁶⁶ Natali¹⁶⁷ and others). Sometimes the reverse may occur, i.e., the ability of storing may be reduced through "functional elimination" (immunization with streptococcus vaccine, Paschkis¹⁶⁸). A local blockade of a restricted group of histiocytes seems also to be possible (Kusnetzowsky,¹⁶⁹ Katsunuma and Sumi,¹⁷⁰ Ledingham¹⁷¹). It is difficult to substantiate the idea of the blockade of the histiocytes by morphologic facts. Histiocytes, which already contain a large amount of a vital dye, as carmine, seem to engulf carbon particles in the usual way after an intravenous injection of India ink (Schulemann¹⁷²). The opinions of the various investigators regarding the blockade diverge widely and observations suggesting successful blockade sometimes can be explained in a different way. It is also probable that the blocked histiocytes can recover rapidly without manifesting distinct structural changes (Jungeblut and Berlot¹⁷³).

I have shown that in inflammation the resting wandering cells or histiocytes of the common connective tissue are mobilized to large, free, phagocytic elements, the macrophages or polyblasts. The same can be

163. Nissen, R.: Der Einfluss kolloidaler gelöster Metalle auf die blutbereitenden Organe mit besonderer Berücksichtigung des reticuloendothelialen Systems, *Klin. Wchnschr.* **1**:1986, 1922.

164. Bieling, R., and Isaac, S.: Experimentelle Untersuchungen über intravitale Hämolyse. I. Der Mechanismus der intravitale Hämolyse nach Injektion von hämolytischem Immunsérum, *Ztschr. f. d. ges. exper. Med.* **25**:1, 1921; Experimentelle Untersuchungen über intravitale Hämolyse. II. Der Verlauf der intravitale Hämolyse nach Milzextirpation, *Ztschr. f. d. ges. exper. Med.* **26**:251, 1922.

165. Gay, F., and Clark, A.: Reticulo-endothelial system in Relation to Antibody Formation, *J. A. M. A.* **83**:1296 (Oct. 25) 1924.

166. Elek, L.: Experimentelle Untersuchungen über das retikuloendotheliale System, *Klin. Wchnschr.* **3**:143, 1924.

167. Natali, O.: Morphologische Untersuchungen über die Bedeutung des retikuloendothelialen Systems bei intravitale Hämolyse, *Ztschr. f. d. ges. exper. Med.* **47**:223, 1925.

168. Paschkis, K.: Zur Biologie des retikuloendothelialen Apparates. I. Kritische und experimentelle Studien zur Funktion und zur Blockadefrage. Retikuloendothel und Immunkörperbildung, *Ztschr. f. d. ges. exper. Med.* **43**:175, 1924.

169. Kusnetzowsky, N.: Ueber vitale Färbung von Bindegewebszellen bei Fettresorption, *Arch. f. mikr. Anat.* **97**:32, 1923.

170. Katsunuma, S., and Sumi, K.: Cellules réticulo-endothéliales et immunité locale, *Compt. rend. Soc. d. biol.* **91**:1401, 1924.

171. Ledingham, J.: The Rôle of the Reticuloendothelial System of the Cutis in Experimental Vaccinia and other Infections: Experiments with India Ink, *Brit. J. Exper. Path.* **8**:12, 1927.

172. Schulemann, W.: Beiträge zur Vitalfärbung, *Arch. f. mikr. Anat.* **70**:223, 1912.

173. Jungeblut, C., and Berlot, J.: The Rôle of the Reticulo-Endothelial System in Immunity. II and III, *J. Exper. Med.* **43**:613 and 797, 1926.

observed after explantation of tissue fragments containing histiocytes. In certain places of the body, especially in the omentum, many free cells of this kind are produced under physiologic conditions and enter the serous cavities in the form of exudate polyblasts. In the lymph nodes, the bone marrow and the spleen, the histiocytes show similar transformations. In normal conditions, a small quantity of these cells may find its way from here into the lymph or blood (Petersen,¹⁷⁴ Sabin and Doan¹⁷⁵). It is also probable that polyblasts originating in local inflamed areas occasionally may enter the lymph or blood vessels and be carried into the general circulation. In abnormal circumstances, these phenomena may attain an extraordinary development.

Aschoff,¹⁷⁶ Aschoff and Kiyono,¹⁷⁷ Tschaschin¹⁴ and Kiyono¹⁵ have shown that free dye-laden histiocytes may be found in the blood of certain sections of the vascular system in animals stained with vital dyes. They are supposed to originate in the spleen, the liver and the bone marrow, to be carried with the venous blood into the right side of the heart and then into the capillaries of the lungs, through which they cannot pass and which they obstruct. Such cells have probably often been mistaken for macrophages of local endothelial origin. Only a few pass into the general circulation. In the capillaries of the lung they probably disintegrate (Aschoff¹⁷⁸); eventually they may get into the capillary veins and become incorporated into their walls (intima granulomas of Siegmund¹⁷⁹).

Repeated intravenous injections of various colloidal dyes or suspensions, of foreign proteins and products of their decomposition and especially use of two different substances combined (Schittenhelm and Erhardt¹⁸⁰) cause an intense general irritation of the histiocytic system. It manifests itself in the appearance of large numbers of free "macrophages" in the blood of the right side of the heart. Simpson²⁴ believes that they appear in separate "showers." This condition is explained by

174. Petersen, H.: Ueber die Endothelphagozyten des Menschen, *Ztschr. f. Zellforsch. u. mikr. Anat.* **2**:112, 1925.

175. Sabin, F., and Doan, C.: The Presence of Desquamated Endothelial Cells, the So-called Clasmatoocytes, in Normal Mammalian Blood, *J. Exper. Med.* **43**: 823, 1926.

176. Aschoff, L.: Ein Beitrag zur Lehre von den Makrophagen, *Verhandl. d. deutsch. path. Gesellsch.* **16**:107, 1913.

177. Aschoff, L., and Kiyono, K.: Zur Frage der grossen Mononukleären, *Folia hæmat. Arch.* **15**:383, 1913.

178. Aschoff, L.: Bemerkungen zur Physiologie des Lungengewebes, *Ztschr. f. d. ges. exper. Med.* **50**:52, 1926.

179. Siegmund, H.: Ueber das Schicksal eingeschwemmter Reticulo-Endothelien (Bluthistiocyten) in den Lungengefässen. Ein weiterer Beitrag zur Entstehung von Gefässwandgranulomen, *Ztschr. f. d. ges. exper. Med.* **50**:73, 1926.

Masugi,¹⁸⁰ however, as occasional admixture of pericardial exudate with the blood drawn into the syringe after repeated punctures of the heart.

In pathologic conditions in man many observers have described large free histiocytes in the peripheral blood in various infectious diseases, such as malaria, recurrent fever and endocarditis (Schilling,¹⁸¹ Kaznelson,¹⁸² Bittorf,¹⁴⁴ Hess,¹⁴⁵ Simpson,³⁴ Seyderhelm,¹⁸³ Kartaschowa¹⁸⁴ and others). It is doubtful whether a clear distinction from monocytes has been made in all these cases. Sabin and Doan¹⁷⁵ claim that blood histiocytes are always present in normal adult mammalian and human blood. Masugi,¹⁸⁰ on the contrary, believes that, even in infectious diseases, they are merely an agonal sign.

In cases of pronounced histiocytosis in experimental animals as well as in man, it is possible to find convincing pictures of contraction and isolation of fixed histiocytes and of their migration into the venous sinuses in the liver, the spleen and the bone marrow. Both tissue histiocytes and littoral histiocytes undergo this transformation.

D. *Monocytes*.—The monocyte problem should be touched on in connection with the question of the rôle of the histiocytes in general defense reactions. Not only the functions of these elements, but also their histogenesis and their genetic relationships to the other cells of the blood and the connective tissue are still unsettled, in the opinion of the majority.

As has been explained, the monocytes migrate from the blood vessels into the inflamed area and are one of the sources of the polyblasts. But it is probable that, even while circulating in the blood, they also belong to the vast and complex machinery used by the organism to protect itself from disturbances of the chemical and physical equilibrium in the internal medium and from the intrusion of extraneous obnoxious factors.

The morphology of the monocytes has been well known since Ehrlich first specified them under the name of "large mononuclear leukocytes" or "transitional forms." At present the supravital staining method with neutral red and janus green is extensively used for their identification (Simpson³⁴ and Sabin²⁵). They show a roset of fine neutral red granules adjacent to the kidney-shaped, excentrically located nucleus,

180. Masugi, M.: Ueber die Beziehungen zwischen Monozyten und Histiozyten, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:396, 1927.

181. Schilling, V.: Ueber hochgradige Monozytosen mit Makrophagen bei Endocarditis ulcerosa und über die Herkunft der grossen Mononukleären, Ztschr. f. klin. Med. **88**:377, 1919.

182. Kaznelson, P.: Seltene Zellformen des strömenden Blutes (Megakaryozyten, Histiozyten, Endothelzellen), Deutsches Arch. f. klin. Med. **128**:131, 1919.

183. Seyderhelm, I.: Ueber das Vorkommen von Makrophagen im Blute bei einem Fall von Endocarditis ulcerosa, Virchows Arch. f. path. Anat. **243**:462, 1923.

184. Kartaschowa, F.: Ueber Monozyten-Makrophagen im peripheren Blut bei einigen Infektionskrankheiten, Deutsches Arch. f. klin. Med. **146**:226, 1925.

and numerous chondriosomes at the periphery. It must be noted, however, that this "roset" is by no means a specific criterion for the monocytes, as there are cells of transitional types connecting the monocytes with the lymphocytes on one hand and with the free histiocytes or macrophages on the other.

I need not enter into a detailed discussion of the various opinions as to the origin of the monocytes. It is sufficient to mention that some investigators believe that they belong to myeloid tissue and originate there from myeloblasts (those who believe in the so-called dualist theory, as Nägeli¹²⁵) or from peculiar "monoblasts" (Cunningham, Sabin and Doan¹⁸⁵), while others (those who believe in the unitarian theory, as Weidenreich¹⁸⁶ and others) consider them to be merely modified lymphocytes. According to McJunkin¹⁸⁷ and many others, the monocytes originate through mitotic division from common endothelial cells. Aschoff and Kiyono¹⁸⁷ and Kiyono¹³ placed the monocytes in close relation to the histiocytes. They did not even discriminate between the monocytes and the free histiocytes of the blood in their first papers. This idea of the identity of these two types of cells has been taken up by many subsequent authors without criticism (Schilling,¹⁸¹ Weicksel,¹⁸⁸ Weil,¹⁸⁹ Holler,¹⁹⁰ Shiomi,⁹⁴ Schittenhelm and Erhardt,¹⁸³ Paschkis,¹⁹¹ Siegmund¹⁷⁰ and others). It has developed, however, at present into the so-called "trialistic" theory, which claims that the monocytes are an independent type of cell, equivalent to the lymphoid and myeloid elements and that they originate from resting histiocytes (Masugi).

The structural differences between the free histiocytes and the monocytes of the blood are usually distinct. The former are much larger and contain more numerous irregularly scattered neutral red inclusions of various sizes. They also show a much higher ability to store vital dyes. If monocytes develop from histiocytes, the change could be accomplished

185. Cunningham, R.; Sabin, F., and Doan, C.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem Cell in Adult Tissue, *Contrib. Embryol.* 82, Carnegie Inst., Washington 16:227, 1925.

186. Weidenreich, F.: Die Leukozyten und verwandte Zellformen; *Ergebn. d. Anat. u. Entwicklungsgesch.* 19, 1911.

187. McJunkin, F.: The Origin of the Phagocytic Mononuclear Cells of the Peripheral Blood, *Am. J. Anat.* 25:27, 1919.

188. Weicksel, J.: Ueber die grossen Mononukleären und Uebergangsformen, Ehrlichs (Monozyten) und ihr Verhalten bei Tuberkulose, *Med. Klin.* 16:1326, 1920.

189. Weil, P.: Ueber Erythrophagocytose im strömenden Blute, *Folia hæmat. Arch.* 26:27, 1920.

190. Holler, G.: Studien über die Stellung der Monozyten im System der Blutzellen, *Folia hæmat. Arch.* 29:84, 1923.

191. Paschkis, K.: Zur Frage der Abstammung der grossen Mononukleären (Zur Biologie des retikulo-endothelialen Apparates II), *Virchows Arch. f. path. Anat.* 259:316, 1926.

only through mitotic division of the latter. It is by no means easy to demonstrate this phenomenon conclusively; most of the authors who advocate this theory did not do it. Something similar can be seen occasionally in the milky spots of the omentum, where smaller cells arise through mitoses of large free histiocytes. The most conclusive demonstration has been given by my work¹⁹² and that of Shiomi⁹⁴ in cultures of lymphoid tissue. This seems to indicate that the origin of monocytoïd cells from histiocytes or macrophages is, indeed, possible. It is also feasible to admit that the undifferentiated mesenchymal elements of the syncytial reticulum in the blood-forming organs may occasionally develop into free elements of the monocyte type. But this phenomenon cannot be a common occurrence, and, even if the theory is correct, only a relatively small number of monocytes may have this origin.

It is far more probable that, in accordance with the original unitarian point of view, the monocytes are genetically closely related to the lymphocytes. I have shown that in inflammation the lymphocytes rapidly hypertrophy and are transformed into young polyblasts, which are structurally similar to or identical with monocytes and only occasionally display with neutral red a slightly less regular "roset." The same transformation is easily seen in tissue cultures. It is natural, then, to look on the monocytes of the normal blood also as hypertrophied lymphocytes, modified and differentiated for the performance of some special functions in the vascular bed, as a kind of "blood polyblast." This transformation may not happen in the tissue of any special place of the body. It is far more probable that the transformation takes place intravascularly, in the lumen of tortuous venous sinusoids with sluggish circulation, as found especially in the spleen, the liver and the bone marrow. This might also explain why in the general circulation the lymphocytes need not show frequent transitions to the monocytes. In cases of experimentally produced general monocytosis (for instance, after inoculation of rabbits with *Bacillus monocytogenes* isolated by Murray, Webb and Swann¹⁹³), the transitional forms between lymphocytes and monocytes are numerous in the peripheral blood, as well as in the various blood-forming organs.

As the formation of monocytes seems to take place in various regions of the body, the elimination of a special blood-forming organ does not influence the number of monocytes in the general circulation. It is known that splenectomy or atrophy of the spleen does not appreciably affect the monocyte count (Kraus¹⁹⁴).

192. Maximow (footnote 84, third reference).

193. Murray, E.; Webb, R., and Swann, M.: A Disease of Rabbits Characterized by a Large Mononuclear Leucocytosis, Caused by a Hitherto Undescribed *Bacillus Bacterium Monocytogenes* (n. sp.), J. Path. & Bacteriol. **29**:407, 1926.

194. Kraus, E.: Zur Pathologie der Milz, Folia hämat. Arch. **26**:87, 1920.

In inflammation the connective tissue is flooded by countless hematogenous and histogenous polyblasts. In cases of generalized irritations, the reaction manifests itself by an increased accumulation in the blood of cells, instrumental in the defense function, free blood histiocytes and monocytes. The blood histiocytes may be compared to the large polyblasts of local origin in inflammation, the monocytes to the polyblasts of hematogenous, lymphocytic origin. As in inflammation the polyblasts of local and hematogenous origin soon lose their differences in the blood with high grade monocytosis and histiocytosis, a complete series of transitional forms connects lymphocytes and monocytes, on the one hand, and monocytes and histiocytes, on the other.

These considerations give a simple explanation to the presumed rapid proliferation of cells in certain vascular areas (especially in the lungs) in different pathologic conditions, such as general infections, or anaphylactic shock (Oeller,³⁶ Töppich,³⁷ Siegmund³⁸ and others). It is clear that there cannot be a question of a proliferation of "cells of the blood vessel walls," which would give rise to countless new cells in the course of minutes. Instead, this accumulation of new cells is due to rapid changes in the distribution of the circulating cells, especially of the monocytes and histiocytes, and to rapid polyblastic transformation of the blood lymphocytes. In this way groups of macrophages may arise in the shortest time on the free surface of the intima of the veins.

Thus the nature of the monocytes is neither lymphoid nor myeloid, nor are they to be considered as a special cell type in the triadistic sense. They are for the most part further stages of development of the ubiquitous lymphoid cells, lymphocytes or hemocytoblasts. In adapting themselves to special functions, probably similar to the functions of the polyblasts on the field of inflammation, they lose a part of the developmental potencies of the lymphocyte. They carry out an important part of the general defense function, but they are incapable of hemopoiesis. Under physiologic conditions their formation is kept in modest limits, and they remain sharply separated from the rare blood histiocytes, which probably serve the same functional purposes. In pathologic conditions, they, as well as the free blood histiocytes, are produced in large numbers, and the sharp distinction between these two cell types disappears simultaneously.

EMBRYONIC, UNDIFFERENTIATED ELEMENTS IN THE CONNECTIVE TISSUE OF THE ADULT ORGANISM

Function acts as a stimulus on the living substance of the cells involved and may cause growth and multiplication. The stimuli calling forth the various defense reactions of the connective tissue, the "mesenchyme," which I have described, "activate" it (Siegmund²²). This "activation" is supposed to be stimulated, for example, by the so-called

"unspecific protein therapy." It manifests itself in the increased production of cells that are instrumental in the various processes leading to the neutralization, digestion and elimination of the foreign substances. The special granulocytes appear in large numbers in the blood, in the inflamed area and develop with increased rapidity in the myeloid tissue. The phagocytic and storing histiocytes in localized areas or all over the body swell, hypertrophy and also increase in numbers. The latter phenomenon is easily observed in the liver. Under physiologic conditions, the walls of the intralobular capillaries show a relatively small quantity of stellate cells among numerous quiescent, small elements. In inflamed areas of the liver or in general stimulation of the whole organ, the number of Kupffer cells may increase to such an extent that they seem to form the only constituent of the wall of the capillary. In the reticulum of the lymphoid tissue of vitally stained animals, the large, phagocytic reticular cells which store the dye, the typical histiocytes, can be distinguished from small, pale elements of the syncytium, which contain few or no inclusions and are especially distinct in the germ centers (Maximow¹⁹²). In inflammation of the lymph nodes, the quantity of the phagocytic, storing, ameboid histiocytes increases at the expense of the smaller, paler elements. The same condition can be found in tissue cultures. Lang¹⁵⁶ has shown that the "dust cells" of the parenchyma of the lung originate from small, inconspicuous elements located in the interalveolar septums, and that their number enormously increases in inflammation and after explantation. The list of such examples could be prolonged still farther. It is clear that under the influence of stimulation the area of the "active mesenchyme" in the adult body enlarges.

This rapid increase of the quantity of active elements, which is so important for the success of the defense reaction, cannot be due solely to the homoplastic multiplication of the active cells already present under physiologic conditions. It is known that in cases of acute increase of hematopoiesis, the usual homoplastic proliferation of the various elements of the blood is accompanied by heteroplastic neoformation of the specific type of cell from undifferentiated stem cells. A similar phenomenon is observed in inflammation or in acute general reactions of the connective tissue. The polyblasts of local histiocytic origin are rapidly joined by uncounted numbers of hematogenous polyblasts which develop from undifferentiated elements, the lymphocytes, through individual differentiation. The quantity of histiocytes in the common connective tissue or in the blood-forming organs, the liver and other organs rapidly increases in cases of need, through additional transformation of undifferentiated elements. These are scattered everywhere between the histiocytes in the reticulum of the blood-forming organs or are arranged

along the blood vessels in the common connective tissue and in the serous membranes.

The connective tissue and the blood of the adult organism contain not only specific cellular elements, more or less differentiated in a given direction for the fulfilment of certain functions, but also undifferentiated elements which keep their original mesenchymal potencies in an unchanged, unrestricted condition. Their existence in the blood-forming organs is a familiar idea. The heteroplastic neoformation of lymphocytes, granulocytes and erythroblasts from stem cells is generally recognized. The only discrepancies are in regard to the nature of these stem cells and especially in regard to the relations between the stem cells of the lymphoid and myeloid tissue. The so-called unitarian theory, which has gained ground decidedly in recent years, claims that there is only one stem cell and that the common small lymphocyte of the blood, therefore, is a cell with full mesenchymal developmental possibilities. This embryonic cell circulates everywhere in the body with the blood and the lymph and, under suitable external conditions, may give rise to any kind of cells of the connective tissue or of the blood anywhere in the body.

Contrary to a widespread opinion, the histiocytes and monocytes, the most important elements in the various defense reactions, cannot be looked on as possessing full embryonic potencies. They certainly have wider possibilities than the fibroblasts or the endothelium. They may be transformed into various cell types and finally into fibroblasts. But their hemopoietic potency has never been conclusively demonstrated. Their potencies of development have been partly and irreversibly restricted as compared with those of the lymphocytes.

Recent investigations have shown that among the fixed cells of the common connective tissue, as well as in the reticulum of the blood-forming organs, there are fixed undifferentiated cells which keep their embryonic mesenchymal potencies (Maximow¹⁹⁵). Everywhere in the reticulum they form the cellular syncytium which accompanies the fibers and contains pale, small, oval nuclei. They are accumulated in large masses in the germ centers, and here, in certain periods, it is easy to watch their transformation into free lymphocytes, the free mesenchymal cells of the adult organism. When myeloid metaplasia occurs, these elements, especially those adjacent to the wall of the capillaries, may, as has been seen, be transformed directly into myelocytes (Lang¹⁸⁹).

In the common connective tissue and in the omentum they are arranged especially along the smaller blood vessels in the form of the so-called "pericytes." Under physiologic conditions they remain quiescent

195. Maximow, A.: Ueber undifferenzierte Blutzellen und mesenchymale Keimlager im erwachsenen Organismus, *Klin. Wchnschr.* 5:2193, 1926.

for an indefinite time. In case of inflammation or other stimulus they awake, recede from the vessels and differentiate into hemocytes, histiocytes or fibrocytes.

Thus on the one hand the mechanism used by the organism for the mesenchymal reactions comprises differentiated cells already fully adapted to the specific function and kept always in readiness. On the other hand, vast possibilities are given everywhere for additional neoformation of such cells by the ubiquitous presence of fixed, undifferentiated mesenchymal elements in the diffuse connective tissue and of free undifferentiated mesenchymal cells, the lymphocytes or hemocytoblasts circulating in the blood and in the lymph.

Notes and News

University News, Promotions, Resignations, Appointments and Elections.

Frank A. McJunkin, associate professor of pathology in the school of medicine of Washington University, St. Louis, has resigned to accept the professorship of pathology and public health in Loyola University, Chicago.

Howard McCordock, holder of a fellowship in medicine (pathology) of the National Research Council for three years, has been appointed assistant professor in pathology in the school of medicine of Washington University, St. Louis.

In the department of pathology of Washington University, St. Louis, Samuel H. Gray has been promoted from instructor to assistant professor and Walter J. Siebert from assistant to instructor.

M. L. Marshall, bacteriologist in the Michigan Department of Health, has resigned to accept an assistant professorship of bacteriology in the University of California.

Israel Davidsohn has been advanced from resident pathologist to director of laboratories at Mount Sinai Hospital in Philadelphia.

E. H. Kettle, professor of pathology and bacteriology in the Welsh National School of Medicine, has accepted a professorship of pathology in the University of London.

Commercial Pathologic Laboratories in Great Britain.—The British Medical Association has adopted resolutions disapproving of the establishment by trading firms of pathologic laboratories as subsidiary enterprises. The association also requires that in announcements to the medical profession every institution undertaking pathologic examinations must give the name of the registered physician in charge of the laboratory and that each report issued from the laboratory must carry the personal signature of this physician or that of some other registered physician approved by him. This requirement has been adopted in order to secure personal responsibility for the reports.

Teaching Clinical Pathology at Bellevue Hospital.—A pathologist makes ward rounds with a small group of students, not more than six every day for a month, and examines and discusses with the students cases selected because of lesions that can be and are studied in the laboratory by various methods. In this way the supplementation of clinical observations by laboratory methods of examination is especially emphasized among the students. In a hospital as large as Bellevue, a student even in a single month can follow a large range of cases.

Institute for Study of Rheumatism.—An institute for the study of rheumatism has been established in Aix-la-Chapelle, Germany.

J. G. Adami Memorial.—A memorial is to be established at the University of Liverpool as a record of the eminence of J. G. Adami as a pathologist and as vice chancellor of the university. The memorial will take the form of an Adami fellowship in pathology or an Adami library of pathology.

Abstracts from Current Literature

Pathologic Physiology

ACUTE INTESTINAL OBSTRUCTION. W. D. GALCH, H. M. TRUSLER and K. D. AYERS, *Am. J. M. Sc.* **173**:649, 1927.

It is concluded from experiments on dogs that in simple acute obstruction of the small intestine death results from dehydration, reduction of blood chlorides by vomiting and starvation. In acute strangulation, toxemia is the main factor. In simple obstruction, treatment with sodium chloride and water prolongs life, but this treatment is without effect on toxemia resulting from strangulation.

BLOOD CALCIUM DEFICIENCY IN EXPERIMENTAL OBSTRUCTIVE JAUNDICE. W. C. BUCHBINDER and R. KERN, *Am. J. Physiol.* **80**:273, 1927.

Puppies subjected to ligation of the common duct were found to withstand the procedure better and longer than older animals. They showed a progressive decrease of blood serum calcium to about one half of the normal value. While the animals increased in weight, growth and weight lagged below normal, as was shown by a greatly increased rate of growth in one animal in which the flow of bile to the intestine was restored. Growth of the long bones is suggested as a factor in calcium deficiency. Increased irritability of the neuromuscular apparatus was not observed.

In three cases of human jaundice, of different origins, a lowered blood calcium content was observed also, which approached normal with a diminution of the icterus.

H. E. EGGERS.

THE MOTILITY OF THE INTESTINAL TRACT IN EXPERIMENTAL BERIBERI (RATS) AND SCURVY (GUINEA-PIGS). B. A. PLUMMER, *Am. J. Physiol.* **80**:278, 1927.

A total absence of vitamin B from the diet of rats resulted in a diminution of the time during which excised intestinal strips showed spontaneous contractions in oxygenated Locke's solution. Amplitude and rate of the rhythmic contractions were markedly decreased in the spastic stage of beriberi in the rats, especially in segments from the duodenum and ileum. Muscular tone was also lessened. Unlike the intestinal strips from normal rats, those from the rats with beriberi showed no resumption of muscular activity after having been kept on ice for twenty-four hours.

In advanced scurvy in the guinea-pig, lessened duration of the period of spontaneous activity was likewise observed. The number of rhythmic contractions was diminished, except in the ileum, where the reverse occurred. Amplitude was increased, indicating hypermotility in the colon and to a slight extent in the duodenum. Tonus was markedly increased.

These results do not agree with observations on the emptying time of the stomach in scorbutic guinea-pigs. The discrepancy is explained on the basis of partial impairment in motility to less than the extent covered by the natural factor of safety.

H. E. EGGERS.

BLOOD CALCIUM AS AFFECTED BY INSULIN. J. C. BROUGHER, *Am. J. Physiol.* **80**:411, 1927.

Following the administration of insulin, the blood calcium both in normal and in parathyroidectomized dogs was found increased for a period of two and one half hours.

H. E. EGGERS.

AN EXPERIMENTAL STUDY OF OSTRUCTIVE JAUNDICE WITH PARTICULAR REFERENCE TO THE INITIAL BILIRUBINEMIA. J. L. BOLLMAN, C. SHEARD and F. C. MANN, *Am. J. Physiol.* **80**:461, 1927.

Following ligation of the common duct in dogs, after extirpation of the gallbladder, an immediate rise in blood bilirubin was observed, which continued to increase uniformly for several hours after the operation. The maximal pressure within the common duct was obtained almost at once, and the progressive rise of bilirubin in the blood followed the maintenance of this pressure. Even with submaximal pressure within the common duct, there was enough retention of bile pigment in spite of continued bile excretion to cause the appearance of increased bilirubin in the blood. The authors deduce that it is the increased intraductal pressure that incapacitates the liver cells so that they no longer absorb the bile pigment from the blood stream, with resultant retention of it there.

H. E. EGGERS.

PHARMACODYNAMIC ACTIONS OF BACTERIAL POISONS. K. K. KOESSLER, J. H. LEWIS and J. A. WALKER, *Arch. Int. Med.* **39**:188, 1927.

Filtrates from bacterial growth were studied for their action on arteries and bronchi. The mixture of micro-organisms contained in bronchial secretions (sputum), empyema fluid, tonsils and other foci of infection, when grown in a blood-broth-glycerol-amino-acid medium, forms substances that cause arterial constriction in vitro bronchial constriction in the living pithed guinea-pig. Certain strains of many common pathogenic micro-organisms—pneumococci, streptococci, *B. coli*, *B. typhosus* and *B. paratyphosus*—form substances with the same effect. The action of the poisons is frequently a selective one. A filtrate that causes bronchiolar constriction may have no action on the smooth musculature of the arteries and vice versa. A spasm of both bronchi and arteries is, however, frequently obtained with the same filtrate. Some poisons causing arterial constriction in vitro cause a marked rise in blood pressure in vivo, thus exhibiting an epinephrine-like behavior. Others that cause constriction of the arteries in vitro lead to a fall of blood pressure in vivo, acting like histamine. The active substances formed are chemically identifiable only in a small percentage. In the majority of cases one has to deal with poisons of unknown chemical constitution. The chemical behavior of the active fraction of the bacterial filtrate suggests that these substances are probably amines. The bacterial poisons studied may be involved in the production of certain forms of bronchiolar spasm in man (bacterial asthma) and others in the production of certain forms of arterial hypertension.

Author's Summary (S. A. LEVINSON.)

CARDIAC OUTPUT IN THE DOG DURING ETHER ANESTHESIA: 1. THE EFFECT OF ETHER ANESTHESIA ON THE CARDIAC OUTPUT, A. BLALOCK, *Arch. Surg.* **14**: 732, 1927. 2. THE EFFECT OF THE INJECTION OF ALKALI ON THE CARDIAC OUTPUT OF THE ANESTHETIZED DOG. A. BLALOCK, *ibid.*, p. 921.

In dogs the cardiac output is increased an average of 76 per cent under ether anesthesia. This is associated with a decrease in the oxygen coefficient

of utilization. The H-ion concentration of the blood increases and the carbon-dioxide content decreases. Under profound anesthesia, the cardiac output is diminished.

In five experiments, the percentage change in cardiac output was plus 196, plus 75, plus 70, and plus 45; while the corresponding figures following the injection of alkali were plus 22, plus 32, plus 49 and plus 3. In the experiment in which the degree of anesthesia was deep, the decrease in the cardiac output during the control period was 8 per cent, and 38 per cent following the injection of alkali.

N. ENZER.

EXPERIMENTAL CHRONIC DUODENAL OBSTRUCTION. B. N. BERG, F. L. MELENEY and J. W. JOBBING, Arch. Surg. **14**:752, 1927.

Duodenal obstruction about 15 cm. from the pylorus was produced in dogs by partially occluding the lumen of the duodenum with a fascial flap mobilized from the posterior sheath of the rectus. Dilatation and hypertrophy proximal to the obstruction followed. Five of twelve dogs were alive after from 174 to 240 days. The other seven lived from 59 to 190 days. Four became emaciated and two developed acute ileus before death. Only occasional vomiting occurred, but no signs of intoxication.

By fluoroscopic examination, dilatation and stasis in the duodenum were confirmed and marked peristalsis with active reverse motility was observed.

Aerobic and anaerobic cultures were made of duodenal contents in normal dogs, and of twenty-five only one was sterile—the others contained *B. welchii*, a nonhemolytic streptococcus and *B. coli*. *B. welchii* occurred alone in seven dogs. After partial obstruction the organisms increased in direct proportion to the degree of obstruction and dilatation, *B. coli* generally becoming most prominent. In six of eleven dogs, the bile was found to contain organisms. In more than half of the animals, the gut distal to the obstruction contained fewer viable organisms. Although the duodenal fluid maintained its rich flora for a considerable period, a distinct fall in the number of bacteria ensued in some cases. The authors suggest the possibility of acquired immunity of the wall of the duodenum to account for this.

N. ENZER.

BLOOD GUANIDINE IN TETANY FROM PARATHYROIDECTOMY. R. H. MAJOR, T. G. ORR and C. J. WEBER, Bull. Johns Hopkins Hosp. **40**:287, 1927.

Increase in blood guanidine could not be detected as a rule.

THE MECHANISM OF THE GALLBLADDER AND ITS RELATION TO CHOLELITHIASIS. LESTER R. WHITAKER, J. A. M. A. **88**:1542, 1927.

The contents of the normal gallbladder are expelled by the activity of its musculature during the digestion and absorption of fat. Proof does not exist that this effect is brought about by a reciprocal action between the sphincter of the common bile duct and the gallbladder; in fact, there is considerable evidence against it.

Stones can be produced experimentally in animals by interference with the normal mechanism for filling and emptying the gallbladder, resulting in stasis and overconcentration of bile. It is possible that stones are produced in human beings by dietetic habits resulting in stasis. It is also possible that debilitating diseases, by reducing the muscle tonus of the gallbladder, favor stasis and the formation of stones.

Stones can be forced out of the gallbladder in experimental animals by the giving of fat. It is probable that the same effect can be produced in human beings by the same means, provided the stones are not too large or the disease has not progressed far enough to render the musculature of the gallbladder ineffective.

THE ROLE OF THE THYROID AND PARATHYROID GLANDS IN THE CHEMICAL DIFFERENTIATION OF BONE DURING GROWTH. F. S. HAMMET, *J. Biol. Chem.* **72**:505, 527, 1927.

Thyroid and parathyroid deficiencies produce distinct types of distortion of the chemical differentiation of bone, with respect to ash, organic matter and water, during growth. Using the percentage of ash as the index of ossification, both types of glandular deficiency produce a lesser degree of ossification than that found in bones of animals of the same age that have not been operated on. Most of this is determined by the retardation of growth of the bone. On the basis of the stage of development as expressed by the weight of the bone, it is only in the case of parathyroid deficiency in the female that ossification is less in degree than normal. Parathyroid deficiency initiated during the pubertal adjustment in the male, conditions a decisive shift in chemical differentiation. This is traceable to the increased sex-specific sensitivity of the organism as a whole.

A distortion of chemical differentiation of bone with respect to calcium, magnesium and phosphorus follows thyroparathyroidectomy and parathyroidectomy in albino rats. The nature of the distortion is the same in both groups, but less in degree in the former. It produces a bone of lower calcium and phosphorus, and a higher magnesium percentage than that normal for the age. The ash has a higher magnesium and phosphorus, and a lower calcium percentage. The shifts in the thyroparathyroidectomized groups are attributable to the parathyroid deficiency. From the point of view of the growth of the bone, however, the specific influence of parathyroid deficiency on calcium increment is not exhibited when the thyroid is likewise lacking. On the basis of stage of development as expressed by the weight of the bone the deviations from the expected percentage values are in general the same in kind as those for ash and are similarly interpretable. Parathyroid deficiency over long periods does not result in decalcification of the bones. A particularly important phenomenon is the relatively greater disturbance of the magnesium fraction.

AUTHOR'S SUMMARY.

A SEASONAL OCCURRENCE OF KETONURIA IN FASTING RATS ACCOMPANIED BY CHANGES IN CARBOHYDRATE METABOLISM. C. F. CORI and G. T. CORI, *J. Biol. Chem.* **72**:615, 1927.

The rate of excretion of acetone bodies by fasting rats is three times as great in summer as in winter, possibly due to a decrease in the functional activity of the pancreas during the summer weather.

ARTHUR LOCKE.

CHANGES IN CARBONDIOXIDE TENSION AND HYDROGEN ION CONCENTRATION OF THE BLOOD FOLLOWING MULTIPLE PULMONARY EMBOLISM. C. A. L. BINGER and R. L. MOORE, *J. Exper. Med.* **44**:633, 1927.

THE EFFECT OF MULTIPLE EMBOLI OF THE CAPILLARIES AND ARTERIOLES OF ONE LUNG. C. A. L. BINGER, D. BOYD and R. L. MOORE, *Ibid* p. 643.

OBSERVATIONS ON RESISTANCE TO THE FLOW OF BLOOD TO AND FROM THE LUNGS.

R. L. MOORE and C. A. L. BINGER, *Ibid* p. 655.

Multiple embolism of the pulmonary capillaries and arterioles is produced by intravenous injection of a potato starch suspension. This results in rapid, shallow breathing and a decrease in the oxygen content of the arterial blood. Maintenance of oxygen saturation by means of oxygen does not prevent the rapid, shallow breathing. Carbon dioxide partial pressure and hydrogen ion concentration in the blood may rise also, but this rise is not constant. Carbon dioxide alone produces rapid, deep respiration.

Embolism of the left lung by direct intra-arterial injection did not produce rapid, shallow breathing. Experimental embolism of the right lung, after ligation or temporary compression of the left pulmonary artery, produced rapid and shallow respiration. Reestablishment of circulation in the left lung restored the normal rate in one animal whose left lung was shown to be normal on postmortem examination, slowed the respiration in some, and did not affect the rate in others. Autopsy in one of the animals in the latter group showed marked hyperemia of the left lung. Neither the oxygen, nor the carbon dioxide, content nor the hydrogen-ion concentration of the blood could be correlated with these variations in behavior.

Multiple pulmonary embolism produces marked dilatation of the pulmonary artery and enlargement of the right side of the heart, as shown by the roentgen ray and by direct inspection after opening the chest during life.

Sudden closure of the left pulmonary artery in dogs and cats does not produce any change in respirations. Gradual compression of the pulmonary artery does not cause change in breathing short of complete stoppage. Gradual compression of the pulmonary veins in cats gives the same result.

Methods of injection into the left pulmonary artery and of compression of the artery with a pneumatic cuff after reclosure of the thorax are described in detail. The Drinker exposed heart technic was used in the experiments on cats.

It is concluded that the exact cause of the rapid, shallow breathing which is considered analogous to that in pneumonia remains unsolved, although the problem has been narrowed down.

R. D. LILLIE.

OXYGEN POISONING IN MAMMALS. CARL A. L. BINGER, JAMES M. FAULKNER and RICHMOND L. MOORE. *J. Exper. Med.* 45:849, 1927.

Oxygen in concentrations of over 70 per cent of an atmosphere is poisonous to dogs, rabbits, guinea-pigs and mice. The poisonous effects manifest themselves in drowsiness, anorexia, loss of weight, increasing dyspnea, cyanosis and death from lack of oxygen. The cause of the lack of oxygen is a destructive lesion of the lungs. The lesion may be characterized grossly as a hemorrhagic edema. Microscopically, there are to be seen in varying degrees of intensity (a) capillary engorgement with hemorrhage, (b) the presence of interstitial and intra-alveolar serum, (c) hypertrophy and desquamation of alveolar cells and (d) interstitial and alveolar infiltration of mononuclear cells. The type of tissue reaction is not characteristic of an infectious process and organisms have not been recovered at autopsy from the heart blood or by puncture of the lung. The poisonous effects of inhalations of mixtures rich in oxygen do not appear to be related to impurities in the oxygen, nor are they related to faulty ventilation, excessive moisture or increased carbon dioxide in the atmosphere of the chambers in which the experimental animals are confined.

AUTHOR'S SUMMARY.

PRESENT STATUS OF CHOLECYSTOGRAPHY AND REMARKS ON THE MECHANISM OF EMPTYING OF THE GALL-BLADDER. E. A. GRAHAM, Surg. Gynec. Obst. **44**:153, 1927.

Cholecystography has been in use for three years. It is a valuable means for studying the functional activity of the gallbladder and affords evidence of even early and comparatively mild inflammatory processes. Not only has it been useful in diagnosing cholecystitis, but it has also been the means of recognizing many more cases of calculi than has been possible by the ordinary roentgen-ray examination, of revealing pericholecystitis and pericholecystic adhesion, of positively identifying shadows seen on a plain film as being related to the gallbladder or not, and of showing various anomalies and abnormalities, such as diverticula, double gallbladder, etc. Of 446 cases reported in the literature, including 147 of the author's, in which gallbladders diagnosed as pathologic by cholecystography were examined at operation, microscopically, only 10 were found not to corroborate the roentgen-ray diagnosis, the percentage of accuracy being 97.8 per cent. In discussing the mechanism of emptying, the author is still of the opinion that the gallbladder empties through the cystic duct by the washing out of its contents by bile from the liver, by the elasticity or contractile mechanism of its walls and by variations of intra-abdominal pressure. Intrinsic contractions of muscle may be a factor, but the leading rôle cannot be ascribed to muscular contractions.

M. L. PARKER.

EXPERIMENTAL GOITER IN RATS UNRELATED IN ORIGIN TO IODINE. ROBERT McGARRISON, *Lancet* **1**:916, 1927.

An actively secretory hyperplasia of the thyroid may develop in young rats on a diet which includes more than 60 per cent of white flour or vitamin, is poor in carbohydrate, and contains 20 per cent or less of protein and inorganic salts, including iodine in adequate amounts, but no green vegetables or fruit. If the process continues, fibrous replacement of thyroid tissue may result. It is suggested that this kind of goiter may develop in people who use white flour.

THE ACTION OF GLUCOSONE ON NORMAL ANIMALS (MICE) AND ITS POSSIBLE SIGNIFICANCE IN METABOLISM. A. Hynd, *Proc. Roy. Soc. B* **101**:244, 1927.

Glucosone is an oxidation product of glucose having the structure: $\text{CHO.CO. (CHOH)}_4\text{CH}_2\text{OH}$. It produces a condition similar to that of "insulin hypoglycemia" on subcutaneous injection into mice, an effect which may be specific and not toxic as it is not produced by the injection of lactosone or of maltosone. The development of the symptoms is modified or inhibited by both epinephrine and pituitrin, and also by sodium acetoacetate, but is not retarded by the administration of dextrose. Glucosone may be an important intermediate in fat and carbohydrate metabolism. It is probably formed by an oxidase-like action of insulin on the blood sugar.

ARTHUR LOCKE.

THE EFFECT OF THE PARATHYROID HORMONE ON THE EXCRETION OF LEAD AND OF CALCIUM IN PATIENTS SUFFERING FROM LEAD POISONING. D. HUNTER AND J. C. AUB, *Quart. J. Med.* **78**:123, 1927.

In lead poisoning, parathyroid extract increased the calcium excretion associated usually with a rise in blood calcium. With the first dose of para-

thyroid hormone the excretion of lead was increased, and this far exceeded the amount excreted under the influence of ammonium chloride and phosphoric acid. The excretion continued for five or six days, but a repeated dose caused little or no increase in the lead excretion, although the calcium output was increased. These studies confirm previous work, showing the similarity between the storage and excretion of calcium and of lead. The rapid liberation of large amounts of lead produced no ill effects.

N. ENZER.

MODIFICATION OF PERMEABILITY OF TISSUES BY ROENTGEN RAY. MME TSEBRIKOW, *Arch. Internat de méd. Exper.* **3**:185, 1927.

The electrical resistance of tissues was determined to find out their permeability. When cancer tissue is planted into a mouse, the specific constant for electrical resistance of the tissues of that mouse is lowered. Cancer tissue itself has a lower value than normal tissue. The constant of normal tissue is lowered by the roentgen ray; the effect is maximum with strong doses of powerful rays and is most marked fifteen days after three hours of radiation. The diminution of electrical resistance by the roentgen ray is more marked in cancerous than in normal tissue.

N. ENZER.

THE EFFECT OF THE ROENTGEN RAY ON BLOOD VESSELS. N. W. LAZAREW, *Strahlentherapie* **25**:255, 1927.

The ears of rabbits were exposed to roentgen rays (60 kilovolt, 2 milliamperes, 1.0 aluminum, 23 cm. faradic skin dose, 23 minutes = 150 per cent erythema dose), and in various intervals (from five minutes to three months) following the irradiation, the ears were half submerged in hot water at 53 C. or 0.3 cc. of croton oil applied to the upper half. Both procedures caused hyperemia and inflammation of the normal ears; it appeared that the ears which were treated showed a higher degree of inflammation if this was provoked within two weeks after the exposure. Within an interval of from two to five weeks, no difference could be noted; an interval of from five to eight weeks, however, brought out a more severe reaction in the ears which were previously irradiated as compared with those of the controls, and also with the reaction observed within two weeks after irradiation. The roentgen-ray reaction in the ears of rabbits appears, therefore, evidently in two cycles; one represents the early reaction and the second one the true reaction. The first period is a constant while the second may not be present, chiefly if a small dose of roentgen rays has been used.

E. A. POHLE.

Pathologic Anatomy

KRUKENBERG TUMORS AND THEIR PRACTICAL PROBLEMS. J. JARCHO, *Am. J. Obst. & Gynec.* **13**:288, 1927.

Jarcho reviews the literature and reports seven cases of so-called Krukenberg tumors of the ovaries, six of which were known to be associated with primary gastric malignancy. Grossly, they presented the typical appearances ascribed to this type of ovarian tumor. Three of the patients were operated on for tumor of the adnexa. In the remaining four, the symptoms referred chiefly to the gastro-intestinal tract and the ovarian tumors were first recognized at necropsy. The author presents evidence favoring a retrograde propo-

gation of gastric carcinoma through the retroperitoneal lymphatics. There is no particular selectivity of the tumor for the ovaries. Other portions of the internal genitalia and bladder may be involved simultaneously.

A. J. KOBAK.

SICKLE CELL ANEMIA. E. V. HAHN and E. B. GILLESPIE, *Arch. Int. Med.* **39**:233, 1927.

The red corpuscles of persons with the "sickle cell trait" are transformed into sickle cells in vitro as a result of asphyxia. The transformation takes place when the oxygen tension falls below a partial pressure of 45 mm. of mercury, provided the hydrogen ion concentration is within certain limits, probably always on the acid side of p_H 7.4. The sickle distortion is a reversible phenomenon. Oxygen and carbon monoxide restore the discoid form. All of the facts relating to sickle cells are consistent with the hypothesis that the sickle form is stable when the hemoglobin is dissociated, and that the discoid form is stable when the hemoglobin is combined. The influence of hydrogen ion concentration in the sickle reaction is probably related to its influence on the dissociation of oxyhemoglobin. Sickle cell formation in vivo is probably induced or increased by anoxemia. Disease of the heart and lungs probably plays an important rôle in causing excessive hemolysis when it occurs in persons with the sickle cell trait. The only specific cause for active sickle cell anemia is the unique hereditary anomaly of the red corpuscles which predisposes to it. A patient with active cell anemia is reported to have been greatly improved by splenectomy. The spleen probably plays a secondary rôle in the excessive hemolysis of active sickle cell anemia and is damaged in the process, passing through stages of enlargement to ultimate atrophy. The influence of the spleen is not the cause of the sickle cell trait.

From Authors' Summary (S. A. LEVINSON).

FAT EMBOLISM. E. P. LEHMAN and R. M. MOORE, *Arch. Surg.* **14**:621, 1927.

It is evident from the literature that trauma is not the cause of all fat embolism and that fat embolism may possibly be due to some chemical or physical change in the blood which disturbs the normal fine emulsion of the blood fat. The authors find that products of protein decomposition, such as necrotic muscle extract, histamine and peptone, will break down emulsions of oil in water—the rapidity and degree of the breakdown being in inverse ratio to the fineness of the emulsion. This did not occur in the physiologic emulsion of fat in blood, probably because of the fineness of the emulsion. This point is being investigated further.

Fat embolism in the lung was produced by the intravenous injection of ether into dogs. The mechanism in operation, they think is probably the solvent action of ether on the blood fat, with precipitation when the ether reaches the lungs and escapes. Fat emboli also resulted after ether inhalation. In both experiments a previous lipemia was brought about by feeding the animal with cream. The injection of calcium lactate and histamine failed to produce fat emboli.

Dogs tolerate the intravenous injection of cotton-seed oil up to 1.5 cc. per kilogram. If man and dog could be compared, a man of 60 Kg. could tolerate 90 cc. of cotton-seed oil intravenously which is more than the fat content of the marrow of the femur; hence, one should be able to pass all the fat of the marrow of the femur into the blood stream without ill effect.

N. ENZER.

THE UNDESCENDED TESTIS. O. H. WANGENSTEEN, Arch. Surg. **14**:663, 1927.

Loss of germinal epithelium, atrophy of the tubules and apparent increase in interstitial cells follow transplantation of the testicle to the abdominal cavity or inguinal region in adult dogs, but not in prepuberty dogs. Regeneration follows replacement of the organ into the scrotum. Undescended testis in men are nearly always aspermatic, but spermatogenesis will occur if the organ is placed in the scrotal sac without injury to the blood supply. N. ENZER.

EXPERIMENTAL BONE MARROW REACTIONS. GULLI LINDH MULLER, J. Exper. Med. **45**:753, 1927.

In rabbits gum shellac solution stimulates the production of red cells in the marrow. The effect does not seem to be one due to destruction of red cells in the peripheral circulation.

AN EXPERIMENTAL STUDY OF THE LYMPHATIC THEORY OF PANCREATITIS. M. KAUFFMANN, Surg. Gynec. Obst. **44**:15, 1927.

At present there are three possible explanations for the etiology of pancreatitis. The first deals with the conversion of the common bile duct and the duct of Wirsung into one continuous channel, permitting the entrance of infected, or chemically altered, bile into the pancreas. The second deals with the possibility of regurgitation of duodenal contents through the ampulla into the duct of Wirsung. The third relates to the extension of an inflammatory lesion from the adjacent organs, particularly the gallbladder and the bile ducts to the pancreas by way of the lymphatics. A great deal of clinical, anatomic and some experimental work has been done to substantiate the last named theory since Klippel first proposed it in 1899. It has many strong supporters. Kauffmann set out to prove or disprove this theory experimentally, and failed to demonstrate a lymphatic route of infection to the pancreas.

M. L. PARKER.

ACUTE THYROIDITIS. H. M. CLUTE and L. W. SMITH, Surg. Gynec. Obst. **44**:23, 1927.

Cases of acute thyroiditis are extraordinarily rare, as compared with cases of acute suppurative inflammatory processes of any other glandular tissues. Only forty-three cases were reported among 45,953 medical and surgical patients admitted to the Basle Clinic during ten years. Only three of over 3,000 operations on the thyroid at the Lahey Clinic were performed for acute thyroiditis. The infrequency may be explained by the anatomic facts regarding the thyroid. First, it is well encapsulated by the fascial compartments of the neck, there being no communication with adjacent structures, except in cases of persistent thyroglossal duct. Second, the lymphatic system of the thyroid is such that it enables it to be drained to a degree unequaled in any of the other parenchymatous organs. In the third place, certain authors have ascribed a local bactericidal function to the thyroid secretion. Pathologically, acute thyroiditis shows the anatomic changes which acute inflammatory processes elsewhere present, namely, dilatation of the capillaries with diapedesis or even frank hemorrhage. Subsequently, there is leukocytic infiltration which tends to be rather diffuse within the lobule. There is usually a diminution of colloid within the follicles and in its place there tends to appear a granular serous precipitate. Following the diffuse inflammatory reaction, one of two things ordinarily occurs: either the inflammatory process localizes as it does

in other tissues, leading to abscess formation, or it subsides relatively rapidly, leaving a certain residuum, namely, definite foci of lymphocytic infiltration scattered throughout the interlobular stroma. The authors believe that the cellular inflammatory reaction seen in some toxic goiters bears no relationship to the development of hyperplasia. They believe that hyperplastic goiters are more prone to injury, and accordingly they are subject to mild inflammatory processes which on subsiding leave this cellular aftermath. On the other hand, inflammatory processes may have some causal relation in the production of the adenomatous goiter. Infection of the thyroid occurs in one of four ways: (1) by direct extension of some perithyroid infection, (2) by traumatic invasion of the capsule, (3) by extension through a persistent thyroglossal duct or (4) by the blood stream. The latter is probably the most frequent. All the bacteria practically are implicated as possible etiologic agents, although inflammation of the thyroid is frequently preceded by infection of the upper respiratory tract.

M. L. PARKER.

SWELLINGS OF THE MALE BREAST. EDMUND ANDREWS and O. F. KAMPMEIER, *Surg. Gynec. Obst.* 44:30, 1927.

The many papers on neoplasms are inclined to give an erroneous impression of the relative frequency of benign and malignant conditions. Especially does this seem to be true of tumors of the male breast, an idea which the authors try to correct, showing that benign swellings are much more common than malignant ones. They report twenty cases of benign enlargement of the breast, and demonstrate that the gland is far from rudimentary, containing even in old age an elaborate system of patent ducts opening into the skin, which are liable to infection from without.

M. L. PARKER.

BENIGN ADENOMA OF THE KIDNEY. E. S. JUDD and H. E. SIMON, *Surg. Gynec. Obst.* 44:169, 1927.

Judd and Simon review the literature (seven cases) on adenoma of the kidney and add a case of their own. The patient had symptoms of eleven years' duration referable to the kidney. Grossly the kidney was atrophic, and there was a tumor, 13 by 11 by 5 cm., occupying one pole and its mesial border. The growth was nodular, covered by a pearl gray capsule. On section the tissue was yellowish gray and sharply demarcated from the renal substance. No gross evidence of metastasis was visible. Microscopically the tumor tissue consisted of papular and tubular structures, formed of cuboidal or low columnar cells with granular protoplasm, large nucleus and definite nucleolus, uniformly arranged on a basement membrane. Mitotic figures were rare, and little fat was present in any of the cells. The tubules were uniform in type and were separated by little connective tissue. In other areas the cells were similar in character and appearance, but they were arranged on papillary projections of connective tissue. Small benign adenomas of the kidney are not uncommon at necropsy, where they are seen varying in size from a few millimeters to 3 or 4 cm. in diameter. They are frequently multiple and may occur in one or both kidneys in the same person. Tumors of this size and type produce no clinical symptoms. Rarely do they become large, producing fairly severe renal symptoms. Histologically, the small and large tumors are similar and occur in three types, papillary, tubular, and alveolar, the first being most common. These tumors arise from the renal parenchyma, and their relationship to malignancy is not definitely established.

M. L. PARKER.

FIBROMYXOSARCOMA OF THE STOMACH IN A CASE OF NEUROFIBROMATOSIS. HANS HARTMAN, Surg. Gynec. Obst. **44**:308, 1927.

Many cases of sarcomatous degeneration of the tumors in the skin or of the nerves with formation of metastases elsewhere, have been reported. Cases of benign neurofibroma of the intestinal tract are few, however, and sarcomatous change occurs even less often. Only four cases of sarcoma arising in a neurofibroma of the gastro-intestinal tract of patients having von Recklinghausen's disease have been recorded in the literature. The author adds another case of sarcoma arising presumably in a previously existing neurofibroma of the stomach wall.

M. L. PARKER.

COMPRESSION OF DUODENUM BY MESENTERY AND THE SUPERIOR MESENTERIC VESSELS. AN UNDERLYING CAUSE OF ACUTE GASTRIC DILATATION. L. H. SLOCUMB, Surg. Gynec. Obst. **44**:359, 1927.

The author discusses the literature, anatomy and mechanics of the subject, and concludes that acute dilatation of the stomach results from compression of the third portion of the duodenum by the mesentery and the superior mesenteric vessels. It never occurs unless atony of the duodenum is present first. It should be looked for in patients with shock, as well as postoperatively. Pre-operative purgation and postoperative administration of morphine are to be avoided.

M. L. PARKER.

THE PITUITARY ADAMANTINOMA. M. CRITCHLEY and R. N. IRONSIDE, Brain **49**:437, 1926.

This uncommon tumor, the pituitary adamantinoma, is described in detail both clinically and anatomically. It produces erosions of the sella turcica, adiposity, infantilism, drowsiness, changes in the optic disk and death with hyperpyrexia. These tumors may arise from epithelial rests, either at the junction of the hypophyseal stalk and the base of the third ventricle, or at the junction of the stalk and the pars anterior. They thus may grow above or below the pituitary diaphragm, producing different secondary destruction. The tumors vary in size between that of a walnut and that of an orange, and are spherical or ovoid. The centers are usually cystic, containing an oily, golden yellow fluid with cholesterol crystals. The walls have papillary excrescences. The solid portion is soft, vascular and deep red. Histologically, the characteristic features are rows of columnar cells corresponding to embryonic ameloblasts arranged in palisade formation at the periphery of epithelial masses. Beneath these cells is an intermediate zone of two or three layers of round, polygonal cells corresponding to the intermediate layer of the enamel organ. Within the layer is a collection of loosely packed cells with frequent whorled cell clusters. These may be keratinized; colloid cysts may occur within the epithelial mass. Necrotic changes may be present, as well as calcareous changes and even bony formation. The stroma is composed of loose connective tissue, and in one case neuroglia was present. The surrounding neuroglia forms a capsule about the tumor. The adamantinoma is sharply differentiated histologically from all other tumors arising in this region.

ROY GRINKER.

THE ANATOMIC PATHOLOGICAL BASIS OF THE PARKINSONIAN SYNDROME FOLLOWING EPIDEMIC ENCEPHALITIS. D. McALPINE, Brain **49**:525, 1926.

A review of the literature of postencephalitic parkinsonism reveals almost uniformly severe damage to the substantia nigra. In both acute and chronic

encephalitis, the substantia nigra is most affected. The author describes eight cases of chronic encephalitis in which he found the substantia nigra to be the most constantly affected area. Subacute inflammatory changes were found in the midbrain, even when the disease had lasted a year. Marked gliosis was seen in the affected areas. The globus pallidus did not reveal any noteworthy change. The locus caeruleus was markedly affected, and to this process are attributed the vegetative symptoms.

ROY GRINKER.

ENCEPHALITIS PERIAXIALIS DIFFUSA. T. G. STEWART, J. G. GREENFIELD and M. A. BLANDY, *Brain* 50:1, 1927.

Three new cases of encephalitis periaxialis diffusa are described, two of which revealed unusually marked changes in the basal nuclei and cerebellum. The essential lesion is a diffuse and symmetrical softening of the deep white matter, involving myelin sheaths and axis cylinders. In one case there was a marked neuroglial reaction with many large globoid glia cells and thickening of the adventitial tissue. In two cases perivascular infiltrations were found, in one of which plasma cells were seen. In case 3 the areas of softening seemed to coalesce from small areas about the blood vessels.

ROY GRINKER.

THE ENDOCRINES IN EPILEPSY: A HISTOLOGICAL STUDY. H. I. SCHOU and W. SUSMAN, *Brain* 50:53, 1927.

The authors found in the suprarenal medulla and anterior pituitary a selective destruction of the chromophile cells. The pancreas resembled that found in diabetes with, however, many more hypertrophied islets and less degeneration. Toxic necrosis was noted in the perivascular channels of all the endocrine glands.

ROY GRINKER.

BENIGN POLYP OF THE OESOPHAGUS OF GREAT SIZE. S. C. DYKE, *J. Path. & Bact.* 30:309, 1927.

A large benign polyp of the esophagus is described. The tumor was attached to the anterior wall of the esophagus at the level of the cricoid cartilage by a pedicle with a long linear attachment. The polyp was about 20 cm. in length the lower portion being cleft at the cardia and the longer portion extending into the stomach. The portion in the stomach was ulcerated. Microscopically, the tumor was covered by stratified squamous epithelium similar to that lining the esophagus. The body of the tumor was composed of somewhat edematous areolar connective tissue. Although the esophagus was greatly dilated extreme difficulty was encountered when food was passed into the stomach. Carcinoma of the esophagus with stricture at the cardia was diagnosed from the radiologic examination. The patient died following a gastrostomy.

E. M. HALL.

ENDOMETRIAL GROWTHS IN LAPAROTOMY SCARS. G. W. NICHOLSON, *J. Obst. & Gynec. Brit. Emp.* 33:634, 1926. C. BERKELEY, *Ibid.*, p. 657. V. BONNEY, *Ibid.*, p. 658.

Nicholson concludes that endometrial tumors are acquired accessory uteri. Of the theories which attempt to explain them, the "peritoneal" is the most generally applicable, and its acceptance offers the fewest difficulties. It alone agrees with biologic facts. It has been suggested that desmoid tumors of the

abdominal wall are in reality endometriomas. Nicholson regards these tumors as fibrosarcomas that have the peculiarity of at first appearing as fibromas and recurring from time after time as more malignant sarcomas. They are equally common in the two sexes, do not have connection with a scar, and have nothing to do with endometrial tumors.

Berkeley reports that about three years after cesarean section a small lump appeared at the lower end of the abdominal scar. The tumor gradually increased in size and was always painful, especially when the patient was menstruating. The tumor was excised. The appearance of the stroma and glandular elements resembled closely that of the endometrium.

In Bonney's case a swelling appeared under the skin just below the abdominal incision for hysterotomy. This occurred within a year of the operation; the nodule enlarged and became painful at every menstrual period. On excision the structure was found to be typical of so-called endometrioma.

LARGE BENIGN POLYP OF ESOPHAGUS. S. C. DYKE, J. Path. & Bact. **30**:309, 1927.

The polyp was attached to the wall at the level of the circoïd cartilage and extended to the cardiac orifice through which it protruded. It was about 16 cm. in length and consisted of a huge overgrowth of subepithelial connective tissue with epithelial covering. It caused obstruction which before death was thought to be due to a carcinomatous structure.

THE EPITHELIAL HETEROTOPIAS OF THE ALIMENTARY TRACT. A. L. TAYLOR, J. Path. & Bact. **30**:415, 1927.

Epithelial heterotopia of *congenital* origin occurs with considerable frequency in the alimentary tract. It is limited almost without exception to that portion of the intestine which lies above the level of the ileocecal valve. The *superficial* congenital heterotopias consist in the substitution of a portion of the normal mucous membrane by areas of mucous membrane foreign to that part, but normal to some other intestinal region. They invariably show an adult structure, the only anomaly being one of situation. The *deep* congenital heterotopias may occupy any portion of the thickness of the bowel wall and may produce tumor-like structures of characteristic naked-eye appearance. Microscopically, they possess a varied structure, the most frequent constituent being pancreatic tissue. In all cases they contain only those types of cell which are normally found in some region of the alimentary tract. In some cases, as in adenomyoma, they show a marked lack of differentiation, with evidence of neoplastic activity. The *clinical significance* of the congenital heterotopias is generally small. The great majority are found by accident at routine postmortem examinations. Rare exceptions to this rule are provided by:

(a) The superficial heterotopias of the gastric mucosa in the small intestine and in Meckel's diverticulum, which may be the seat of ulceration with intestinal hemorrhage or perforation.

(b) Certain deep heterotopias of the stomach and small intestine, notably the pyloric adenomyomas. These tumors may produce symptoms suggestive either of gastroduodenal ulceration or cancer, and for which operation may be performed.

(c) Nodules of aberrant pancreas at the apex of Meckel's diverticulum which may produce mechanical obstruction of the intestine.

(d) Certain umbilical polyps, which may cause discomfort or pain and an irritating discharge.

The congenital heterotopias play no part in the production of malignant disease. For this reason local excision only should be practised in all cases requiring operative treatment. Congenital heterotopia is a dysontogenetic and not an atavistic condition. It is a tissue malformation arising from an error of development of the fetal entoderm. In their distribution and in their antimesenteric situation, the congenital heterotopias correspond closely with the diverticula occurring in the intestine of the embryo. It is concluded that they arise from those embryonic diverticula which abnormally persist. The precise nature of the abnormal stimuli which result in their formation is unknown. The superficial heterotopias of *acquired* origin occur chiefly in the stomach and consist of epithelium of intestinal type. They are produced by an error of differentiation in the regenerative process accompanying ulcerative lesions. They spring from the "indifferent" cells normally present, when under abnormal stimulation there is a reappearance of an alternative cell character which was previously latent. The deep heterotopias of acquired origin may be of hyperplastic or regenerative type. The *hyperplastic* type is a rare condition occurring in the stomach by glandular penetration through the vascular gaps in the muscularis mucosae. The *regenerative* type is found in all parts of the alimentary tract in ulcerative lesions where the muscularis mucosa is destroyed. It consists of glandular structures segregated in the submucous tissues during the regenerative process. Evidence is brought forward that the growth of these heterotopias though abnormal in situation is of typical character. Both superficial and deep heterotopias of acquired origin consist of fully differentiated or normally developing tissue. They may coexist with carcinoma but they take no part in its production.

AUTHOR'S SUMMARY.

THE MAGNESIUM CONTENT OF THE CEREBROSPINAL, AND OTHER BODY FLUIDS.

H. COHEN, *Quart. J. Med.* **78**:173, 1927.

The magnesium content of normal cerebrospinal fluid is constantly higher than that of the corresponding contemporary blood serum by an average of from 20 to 30 per cent. It generally is lowered in meningitis and in this respect resembles the chlorine ion. An increase in the magnesium content of the plasma does not affect the content of the spinal fluid. Pleural and peritoneal effusions contain less magnesium than the blood serum.

N. ENZER.

HISTOPHYSIOLOGIC STUDIES ON THE FATE OF OILS INJECTED SUBCUTANEOUSLY.

L. BINET and J. VERNE, *Ann. d'anat. path.* **4**:1, 1927.

Binet and Verne have investigated the fate which different oils undergo when injected subcutaneously. According to their investigations, oil injected under the skin of animals disappears slowly, in fact, seldom before several months have passed. They state that vegetable oils are absorbed quicker than animal oil. The absorption is accompanied by a reaction which consists of mononuclear cells of hematogenous origin and of connective tissue cells. The cells surround the oil droplets, often forming cystlike structures. They also take an active part in the absorption of the fat which undergoes saponification.

B. M. FRIED.

INITIAL LESIONS IN DIABETIC ARTERIES. M. LETULLE, M. LABBÉ and J. HEITZ, *Ann. d'anat. path.* 4:9, 1927.

Letulle, Labbé and Heitz studied the histology of the arteries in two patients with rather grave diabetes, whose disease was apparently of short duration. The tibial arteries in these patients, viewed grossly, showed the vessels to be practically normal, but the microscope revealed sclero-atrophic, insular, chronic panarteritis. Both elastica, the interna and externa, were in entirely destroyed areas; the destruction was obviously due to some active and powerful agent. Likewise, the hyaline degeneration scattered in nests in the muscularis was the result of some kind of an inflammatory process. The authors believe that diabetes is the cause of subacute attacks of panarteritis; this sclero-atrophic panarteritis is, according to their statement, the initial phase of the disease. In instances in which the causative agent is not removed, similar "attacks" lead finally to obliteration of the lumina of the vessels.

B. M. FRIED.

MALIGNANT GRANULOMATOSIS. TITU VASILIU and ION GOIA, *Ann. d'anat. path.* 4:33, 1927.

A good review of Hodgkin's disease, with an abundant bibliography, is presented by two scientists from the University of Cluj, Roumania.

B. M. FRIED.

ADENOMYOMA OF THE FUNDUS OF THE GALLBLADDER. J. L. NICCOOL, *Ann. d'anat. path.* 4:133, 1927.

This is the fifth case of adenomyoma of the gallbladder found by Niccool at necropsy. The four previous cases were described by him in a thesis for the doctorate (*These de Lauzanne*, 1922). The tumor is usually the size of a small pea; it is situated underneath the peritoneum, the surface of which is smooth and regular. The mucosa in the region involved, except for a slight depression, does not show any pathologic change. On cut surface, the tumor is fibrous, whitish and compact, containing small cavities at the periphery. Although it is deprived of any capsule, it does not invade the surrounding tissues. Microscopically, it is roughly composed of three zones: a central glandulotubular zone, a middle muscular zone and an external glandular, cystic zone. The growth, then, is benign and epithelial, originating in the mucosa of the gallbladder. It is apparently not of clinical importance.

B. M. FRIED.

ORIGIN OF MONOCYTES OF THE BLOOD. W. BÜNGELER, *Beitr. z. path. Anat. u. z. allg. Pathol.* 76:181, 1926.

Whether monocytes of the peripheral blood are derived from the hemopoietic tissues of the bone marrow, as some have claimed, or from the histocytes of the reticulo-endothelial system, as a larger number of more recent investigators have asserted, was subjected to experimental study by the author. Rabbits were given repeated intravenous injections of India ink, saccharated iron oxide, collargol or lipoids. Cells of the monocyte type appeared in the blood from two to three hours after such injections and constituted as high as 9 per cent of the total white blood corpuscles after the fourth injection. After the third or fourth injection, monocytes with stored material were present to the extent of from 8 to 10 per cent of all the monocytes. From three fourths to one third of the monocytes gave the oxidase reaction. When animals whose

reticulo-endothelial systems had been filled with the colored substance used received an intravenous injection of egg-albumin as long as four weeks after the last previous injection of pigmented material, monocytes with stored material appeared in the circulating blood, which is interpreted as proof that such cells came from the reticulo-endothelial system. Since from one fourth to one third of the circulating monocytes in Büngeler's experiments gave the oxidase reaction, he concludes that cells other than the granulocytes of myeloid origin may give this reaction.

O. T. SCHULTZ.

EFFECT OF PHOSPHOROUS POISONING ON ADIPOSE TISSUE. N. P. BALAN, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:198, 1926.

The fatty changes caused in the tissues by phosphorus were studied histologically in relation to changes in the adipose tissues. Rats received subcutaneously a single fatal dose varying from 1.5 to 5 mg. in oil. Other animals of the same species were given repeated subcutaneous injections of sublethal doses. Both procedures caused a marked fatty change of the liver cells, renal tubular epithelium, myocardium and skeletal muscle, the deposited lipoids being neutral fats according to their microchemical staining reactions. After single fatal doses no changes could be detected in the adipose tissues, but after repeated smaller doses a characteristic change in the microchemical reactions was noted in the fat of the adipose tissues, indicative of an alteration in the lipid constitution of the fat believed to be the result of the action of phosphorus. The fatty change of the parenchymatous organs is the result of fat storage, due to intracellular synthesis.

O. T. SCHULTZ.

CHANGES IN LIVER TISSUE REMOVED BY BIOPSY. W. ENDERS, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:215, 1926.

As the result of comparative histologic study of tissue removed from the margins of the liver by biopsy with tissue removed from more central portions of the same livers at necropsy, Enders concludes, in agreement with previous work of Metzler, that marginal tissue only exceptionally gives a true picture of changes present throughout the liver. Interlobular fibrosis or lymphocytic infiltration may be present in the marginal tissue readily removed for examination during laparotomy, but the liver as a whole may be free from similar alterations.

O. T. SCHULTZ.

ELASTICITY OF ELASTIC FIBRILS. E. REDENZ, Beitr. z. path. u. z. allg. Pathol. **76**:226, 1926.

The article of Redenz is preceded by a short introductory paper by Petersen, of Würzburg, who states the theoretical objections to the conceptions of Ranke (Abstr., ARCH. PATH. **2**:106 [July] 1926), that tissue elasticity is dependent on the fixed curves of the elastic fibrils. By means of a micromanipulator, Redenz stretched isolated elastic fibrils from the ligamentum nuchae of the ox. When the length of the fibrils was increased 50 per cent, a return to the original length occurred after the force was released, and an increase in length of 100 per cent was followed by almost complete return, indicating a high elasticity of the tissue which was not due to fixed curves or spirals, but to the composition of the material.

O. T. SCHULTZ.

THERMODYNAMICS OF CONNECTIVE TISSUES. E. WÖHLISCH and R. DU MESNIL DE ROCHEMONT, *Beitr. z. path. Anat. u. z. allg. Pathol.* **76**:233, 1926.

This is a further criticism, on an experimental basis, also carried out under the direction of Petersen, of Ranke's conception of tissue elasticity. The latter had established for the aorta curves which he claimed were different from those given by any other known elastic material. The authors obtained comparable curves by application of the laws of thermodynamics to rubber and ligamentum nuchae. Tendon, which has slight elasticity, yielded a curve of a typical elastic material after heating to 60 degrees.

O. T. SCHULTZ.

EXPERIMENTAL CALCIFICATION. W. DREYFUSS, *Beitr. z. path. Anat. u. z. allg. Pathol.* **76**:254, 1926.

This is a repetition of the work of Rabl, who studied calcium deposition in mice maintained on alternating acid and alkaline diets and on acid diets alone, both with an excess of calcium. As the result of this work, he explained calcification on a physical chemical basis, tissue hydrogen ion concentration being most important, and an excess of calcium in the blood, a factor of little importance.

Dreyfuss also used mice, maintaining one series on alternating acid and alkaline diets, another on acid diet alone and another on alkaline diet alone. All received an excess of calcium with the food. Calcium was most marked in animals kept on acid diet and next in animals on alternating acid and alkaline diets. In such animals the chief sites of calcium deposition were the myocardium, the lung and the wall of the stomach. In all the animals of all series, including normal animals, there were numerous calcium cylinders in the collecting tubules of the kidneys, and a tendency to calcium deposition in the bronchial cartilages also appears to be a regular occurrence in mice. Although his results in general confirm those of Rabl, the author believes that the frequency of calcium cylinders in the kidneys and of calcium deposits in the bronchial cartilages of normal mice indicate a calcium metabolism peculiar to this animal, and that the experimental results in mice are not necessarily applicable to other animals or to man, in which an excess of protein-bound calcium in the blood serum may be an important factor in calcification.

O. T. SCHULTZ.

PANCREATIC ISLETS AFTER DUCT LIGATION. G. HERXHEIMER and E. CARPENTIER, *Beitr. z. path. Anat. u. z. allg. Pathol.* **76**:270, 1926.

Herxheimer is of the school which accepts the derivation of the islets of the pancreas from acinar and terminal duct epithelium. He grants that the islets alone are concerned in the elaboration of the internal secretion of the pancreas, but in view of the close relation of island and acinar tissue, holds that diffuse processes not limited to the islets may be a factor in the pathogenesis of diabetes, in that damage to the acinar tissue may prevent a protective or compensatory new formation of islets. In two dogs in which ligation of the duct led to partial atrophy of the pancreas, Mansfeld had reported an increased sugar tolerance during life, an observation which was interpreted as indicating hyperactivity or hyperplasia of the insular tissue with an increased formation of insulin. Herxheimer and Carpentier ligated the pancreatic ducts of chickens, determined the blood sugar at repeated intervals after the operation and studied the pancreas microscopically at the end of the experiment

and determined the insulin content of the organ. In thirteen animals all of the three ducts could not be ligated; in these animals the blood sugar showed no significant changes and the partially atrophic pancreatic tissue did not yield an increased amount of insulin a gram. In one animal, however, which is given detailed discussion, it was possible to ligate all the ducts. In this experiment the blood sugar dropped after the operation, reaching on the eleventh day about one third of the normal level, and hypoglycemic convulsions led to death. The acinar tissue was almost completely atrophic. The islands, on the other hand, were large and numerous, their number being so great as to warrant the assumption of the formation of new islands from acinar tissue. The insulin yield was four times that of the pancreas of normal chickens. The authors interpret the striking results in this experiment as proof of the formation of an excessive amount of functioning islet tissue from acinar tissue.

O. T. SCHULTZ.

THE MICROSCOPIC CHANGES OF LECITHINOID DEGENERATION. T. VON LEHOCZKY, *Virchows Arch. f. path. Anat.* **261**:516, 1926.

In a case of tuberculous meningitis, the author found the same lipid material within the ganglion cells and encrusted on the golgi net as is usually found in amaurotic idiocy. He believes that the presence of this lipid signifies a definite type of degeneration.

ROY GRINKER.

CHANGES IN THE SYMPATHETIC GANGLIONS IN RABIES. S. CHACHINA, *Virchows Arch. f. path. Anat.* **261**:795, 1926.

In cases of rabies, the sympathetic ganglions undergo a diffuse inflammatory process, with marked degenerative changes in the ganglion cell. The intensity of the process does not depend on the period of incubation, or the duration of the disease. The cervical and upper thoracic ganglions were most severely affected, the vertebral more than the sympathetic. The infiltrate about the capsule of the ganglion cells may break through and surround the cells. It is composed of lymphocytes.

ROY GRINKER.

CHANGES IN THE CENTRAL NERVOUS SYSTEM IN RABIES. S. I. KRINITZKY, *Virchows Arch. f. path. Anat.* **261**:802, 1926.

In rabies nothing characteristic is found macroscopically. The leptomeninges are edematous and hyperemic, and contain few leukocytes. In the cortex, sub-cortical ganglions and cerebellum, the ganglion cells are severely degenerated with hyperemia, hemorrhage and edema. Neuronophagia is present throughout, and most marked in Ammon's horn. The most severe process takes place in the pons and medulla—infiltration of the vascular walls with lymphocytes spreading mantle-like into the tissue and severe degeneration of the ganglion cells.

ROY GRINKER.

DISCUSSION OF THE PRIMARY EPITHELIAL TUMORS OF THE CENTRAL NERVOUS SYSTEM. A. GROMELSKI, *Virchows Arch. f. path. Anat.* **261**:933, 1926.

The difference between a choroidal plexus epithelioma and one of ependymal origin is discussed. A case of papillary carcinoma arising from the lumbar sac is described.

ROY GRINKER.

Pathologic Chemistry

A STUDY OF THE COAGULATION OF THE BLOOD: THE CHEMICAL REACTIONS UNDERLYING THE PROCESS. A. B. WADSWORTH, F. MALTANER and E. MALTANER, *Am. J. Physiol.* **80**:502, 1927.

The writers have found that in the coagulation of blood, certain definite chemical reactions take place. First there is a reaction of ionized calcium salts with an active lipoid substance to produce a calcium-lipoid complex and free acid. In the presence of the latter, the proteins of the plasma react with lipoid to produce an insoluble lipoid-protein complex—fibrin. The rôle of the calcium is apparently that of a catalyzer, since the amount required is small, and since it is found in almost undiminished amount in the serum after termination of the clotting process. They suggest that three distinct phases are involved in the process: first, the combination of lipoid with calcium salts, with liberation of the free acid; second, a reaction between the free acid and fibrinogen to produce acid fibrinogen; and, third, a reaction between the acid fibrinogen and the calcium-lipoid complex, with liberation of the calcium in combination with the acid.

H. E. EGGERS.

MINERAL SALT CONTENT OF THE BLOOD IN DISEASE. A. S. BLUMGARTEN and G. L. ROHDENBURG, *Arch. Int. Med.* **39**:372, 1927.

The mineral salt content of the blood was studied in 173 patients suffering from various diseases. The determinations were made on whole blood, both the absolute and the percentage figures being determined, as well as the total salt content. The normal figures for the various salts were as follows:

Absolute	Percentage
Sodium, from 120 to 180 mg. per hundred cubic centimeters.....	40 to 55
Potassium, from 130 to 170 mg. per hundred cubic centimeters.....	35 to 45
Calcium, from 6 to 11 mg. per hundred cubic centimeters.....	2 to 3
Magnesium, from 2.98 to 4 mg. per hundred cubic centimeters.....	1 to 1.5
Total salts, from 250 to 300 mg. per hundred cubic centimeters	

Variation was not noted between the absolute salt content and its percentage of the total salts. The calcium and the magnesium content of the blood usually ran parallel. The most striking pathologic conditions in which a disturbance of the mineral salts in the blood was determined were carcinoma, leukemia and purpura hemorrhagica. In carcinoma a strikingly low magnesium content and a low calcium content were encountered in 50 per cent of the cases, but the tendency toward hypermineralization was not marked. In two of the cases of leukemia and purpura hemorrhagica which were studied, there was a marked reduction in the potassium content and a compensatory increase in the sodium and the calcium content, which the authors believe was probably due to hemorrhage. High magnesium contents were found in arteriosclerosis and in other conditions which usually are associated with advancing years. Chronic nephritis with hypertension showed a low calcium and a high sodium content. Disease of the gallbladder showed a high total salt and a high magnesium content.

AUTHORS' SUMMARY (S. A. Levinson).

A HITHERTO UNSUSPECTED SOURCE OF ARSENIC IN HUMAN ENVIRONMENT. R. E. REMINGTON, *J. Am. Chem. Soc.* **49**:1410, 1927.

The arsenic content of tobacco so far exceeds that of the substances which make up a normal diet that it may be questioned whether the habitual smoker does not possibly expose himself to the danger of chronic arsenic poisoning.

ARTHUR LOCKE.

BLOOD REACTION AND BLOOD GASES IN PNEUMONIA. C. A. L. BINGER, A. BAIRD HASTINGS and JULIUS SENDROY, JR., J. Exper. Med. **45**:1081, 1927.

Evidence of acidosis was not noted at any time during the disease in nineteen cases of pneumonia.

CERTAIN CHEMICAL CHANGES ASSOCIATED WITH GALLSTONES, WITH SPECIAL REFERENCE TO THE RELATION BETWEEN GALLSTONES AND HYPERCHOLESTEROLEMIA. F. S. FOWWEATHER and G. A. COLLINSON, Brit. J. Surg. **14**:583, 1927.

As a result of calcium and cholesterol determinations of the blood, bile, gallbladder and gallstones in eighty-one cases of cholecystectomy, the authors believe that the formation of gallstones is primarily dependent on stasis and concentration of bile, the cholesterol of which crystallizes as stones or is absorbed through the vesical wall into the blood. The variations in the cholesterol content of the blood are secondary to changes in the gallbladder and its contents. The blood cholesterol was definitely increased in 46.7 per cent of the cases, the blood calcium in 32.8 per cent. The bile cholesterol tended to be increased, this tendency decreasing as the blood cholesterol increased. The concentration of calcium in the bile tended to be less than normal. In the gallbladder both cholesterol and calcium were increased. Following cholecystectomy the blood cholesterol returned to normal. Although no particular type of stone was found to be associated with any special type of chemical change in the materials examined, it is suggested that the degree of supersaturation of bile with cholesterol is one of the main factors determining the type of stone that will form.

BENSON BLOOM.

CHEMICAL REACTIONS OF THE LENS. G. BUGLIA, Arch. ital. de biol. **76**:1, 1926.

After death the lens may become opaque, but this opacity disappears on warming, to return on cooling. This phenomenon was found to depend on changes in hydrogen ion concentration and changes in the salt-protein combinations.

STUDIES OF THE INTRACELLULAR FAT GRANULES IN TISSUE CULTURES. K. NAITO,

Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) **4**:279, 1925.

The growth of fibroblasts in tissue culture is enhanced by cholesterol esters and lecithin in the medium, retarded by fatty acids and unaffected by neutral fat and cholesterol. A special unknown fat (possibly an unsaturated glycerol ester) is first formed; this is a forerunner of the neutral fat which changes to phosphatide and then to cholesterol ester. The fibroblast uses the free fat or lipid of the hypotonic plasma medium only after certain physical and chemical changes have occurred, perhaps a breaking down and then a resynthesis within the cell. The decrease of the oxydase granules and the mitochondria of the cell may be related to the increase of fat granules within the cell, but in the author's opinion it is attributable, at least in part, to the use in cell activity.

Microbiology and Parasitology

THE MICROBES IN PYORRHEA ALVEOLARIS. JOHN H. FISHER, Am. J. Path. **3**:169, 1927.

Endamoeba gingivalis was found in 95.5 per cent of 201 cases of pyorrhea; fusiform bacilli and spirilla were found in all the cases; *Streptococcus viridans* (mitis and salivarius) was present in all of thirty cases examined culturally; no hemolytic streptococcus were found.

A NEW ORGANISM THAT MAY BE A FACTOR IN PUERPERAL INFECTION. JOHN W. HARRIS and J. HOWARD BROWN, Bull. Johns Hopkins Hosp. **40**:203, 1927.

From the uterus in puerperal infection as well as from uterine cultures after cesarean section, a strict anaerobe, closely resembling *Actinomyces necrophorus*, has been isolated. The new organism, named *Actinomyces pseudonecrophorus*, is nonhemolytic, does not ferment lactose, and there is no cross-agglutination with immune serums against the necrophorus and the pseudonecrophorus. The history of the patients from which the new organism was obtained indicates that it is not harmless.

COMPARATIVE PATHOLOGY OF SOUTH AFRICAN JAGZIEKTE AND MONTANA PROGRESSIVE PNEUMONIA OF SHEEP. E. V. COWDREY and HADLEIGH MARSH, J. Exper. Med. **45**:571, 1927.

As the cause of these diseases is not known, it cannot be said that they are identical, but they appear to be so, and it is not now possible to distinguish between them.

THE PURPURA-PRODUCING PRINCIPLE OF THE PNEUMOCOCCUS. LOUIS A. JULIANELLE and HOBART A. REIMANN, J. Exper. Med. **45**:609, 1927.

The purpura substance is associated with the proteose fraction of active pneumococcal extracts and is regarded as an autolytic derivative. It does not stimulate the formation of antibodies.

STUDIES ON THE PHYSICAL AND CHEMICAL PROPERTIES OF THE VIRUS OF FOOT-AND-MOUTH DISEASE. PETER K. OLITSKY and LOUIS BOËZ, J. Exper. Med. **45**:673 and 685, 1927.

A strain of virus was carried through at least 261 passages in the guinea-pig. This virus was active in dilutions of 1:10,000,000. The active agent was not sedimented by centrifugalizing, which is the case also with certain other infectious agents. Ordinarily, the virus carries an electropositive charge, thus differing from ordinary bacteria and furnishing an explanation for certain filtration phenomena, which do not support the idea that the virus is a fluid.

BACTERIUM LEPISEPTICUM INFECTION: ITS MODE OF SPREAD AND CONTROL. LESLIE T. WEBSTER and CASPAR BURN, J. Exper. Med. **45**:911, 1927.

In this paper we have attempted to describe the manner of spread of an endemic, native, respiratory infection and a method for its control. The essential factor determining the prevalence of such an endemic disease is, we believe, host susceptibility, which is controlled by hereditary and environmental influences. Furthermore, it seems probable that the amount of this susceptibility of the population determines the dosage of specific microbes available to the population.

An increase in dosage in the herd is followed by an increase in the spread and severity of the infection, and a decrease by a corresponding alleviation. Hence, two methods for the prevention of epidemics are available: (1) an enhancement of the resistance of the population and (2) the reduction to a minimum of available dosage. These procedures have proved successful for three years in maintaining a population of breeding rabbits, in the midst of a badly infected community, entirely free from infection with *Bacterium lepi-septicum*.

AUTHORS' SUMMARY.

RELATION BETWEEN AMINO-ACIDS AND THE WASSERMANN REACTION. F. L. FAIRWEATHER and JOHN GORDON, Brit. J. Exper. Path. **8**:93, 1927.

In experiments in vitro and on rabbits, and in parallel determinations of blood amino-acid nitrogen and Wassermann reaction in syphilitic and nonsyphilitic patients, no relation was found between the amino-acid content of blood and its Wassermann reaction.

TUNGSTEN ARCH AS SOURCE OF ULTRAVIOLET RADIATION. GEO. L. ALEXANDER, Brit. J. Exper. Path. **8**:115, 1927.

The sterilizing effects of ultraviolet rays are emphasized.

RELATIONSHIPS BETWEEN HEAT-STABLE AGGLUTINOGENS AND SENSITIVITY TO BACTERIOPHAGE IN SALMONELLA GROUP. F. M. BURNET, Brit. J. Exper. Path. **8**:121, 1927.

B. enteritidis, *B. typhosus* and *B. pullorum* have practically identical heat-stable agglutinogens and similar types of reaction toward bacteriophage.

MELIOIDOSIS IN COCHIN CHINA. R. PONS and M. ADVIER, J. Hyg. **26**:28, 1927.
MELIOIDOSIS FROM SAIGON. A. T. STANTON and WILLIAM FLETCHER, Ibid. **26**:30, 1927.

In each instance, a septicemic form of human infection with *B. whitmore* is described. Melioidosis (the Greek roots mean glanders-like disease) was described by Whitmore in 1913. It occurs in various animals as well as man, and an instance in a horse is reported by Stanton, Fletcher and Symonds (J. Hyg. **26**:33, 1927).

SPECIFIC TOXICOGENIC PROPERTIES OF HEMOLYTIC STREPTOCOCCI FROM SCARLET FEVER AND OTHER SOURCES. D. G. S. McLACHLAN, J. Hyg. **26**:84, 1927.

A toxic principle which in high dilutions evoked cutaneous reaction in susceptible persons was produced by all of ninety-eight strains of streptococci from scarlet fever. In the majority of strains from other sources with similar toxicogenic properties, this property was weakly developed. In a few instances toxin as active as that of scarlatinal strains was produced.

LEISHMANIASIS IN AMERICA. E. ESCOMEL, Med. Argentina **5**:50, 1926.

In South America there has existed, at least since the Incas, a leishmaniasis which can be differentiated on etiologic, geographic, clinical, pathologic, parasitologic and therapeutic grounds from oriental sore (kala-azar). The American type includes the skin variety, uta, and the cutaneomucous variety, espundia. The disease may last as long as thirty years, involve different systems and cause both secondary and tertiary manifestations. The vector is unknown, but in Peru it may be *Leptus japa*. In some areas, the disease often coexists with a similar clinical condition; namely, blastomycosis caused by the fungus provisionally named *Cryptococcus americanus*.

THE ROADS OF PROPAGATION OF TUBERCULOSIS. B. LANGE, Beitr. z. klin. d. Tuberk. **65**:278, 1926.

Severe infections of man by tactile contact or by the ingestion of infected food may occur only if a large number of tubercle bacilli are introduced through the mucous membranes of the upper respiratory or digestive tract. Bacilli that invade the body through such mucous membranes are apparently weakened

in their pathogenicity, since they usually lead to distinctly benign forms of disease. The infection by inhalation either of dry dust or of bacilliferous droplets is of a much greater practical importance. The author believes that dust infection is much more frequent than droplet infection, since the opportunity for the former is much more readily given.

MAX PINNER.

THE ROADS OF PROPAGATION OF TUBERCULOSIS IN THE BODY. H. BEITZKE, Beitr. z. klin. d. Tuberk. **65**:291, 1926.

Since it has been definitely established that the primary complex is most frequently found in the lung, it is necessary to analyze how bacilli may reach this location. Theoretically, four avenues are possible:

1. A primary deposit in either the upper or lower digestive tract may reach the lung through the lymphatics, thoracic duct, venous blood and right side of the heart.
2. It has been claimed that they may travel from the cervical glands directly to the bronchial glands.
3. It is believed possible that they may be transported from the cervical glands directly to the apical pleura, and from there into the parenchyma.
4. Direct inhalation.

It is, however, certain that there are no lymph vessels leading from the cervical glands to the bronchial glands. It is not possible to inject the tracheo-bronchial glands from the cervical or supraclavicular glands, not even if the lymphatic trunk, before its opening into the vein, is clamped, since valves prevent the retrograde lymphatic stream. In cases in which both cervical and tracheobronchial glands are diseased, it is always observed that the glands decrease in size from the mandibular angle to the venous angle, and increase from here to the tracheobronchial glands, indicating two independent foci of disease. As far as the transpleural way is concerned, it must be remembered that the cervical glands have no connection with the supraclavicular glands, which alone could be held responsible for the pleural infection. In this mechanism, too, the retrograde lymph stream would have to be assumed. If one wishes to assume that the infection of the bronchial glands occurs from the mesenteric or cervical glands, one would have to prove that either one of these glands is always diseased in cases of tuberculous foci in the tracheobronchial glands, since tubercle bacilli always leave their mark on the lymph glands first invaded. The fact that cases in which tubercle bacilli are found in different groups of lymph glands, in a more or less latent condition, are rare is another argument against this mode of propagation. If tubercle bacilli have first to pass lymphatic organs, their virulence is markedly decreased, particularly if they are small in numbers. The lung, however, which is not an organ of resorption, will respond much more readily to a low grade infection than the lymphatic tissue. In short, epidemiologic, experimental and anatomic studies argue strongly in favor of the primary pulmonary infection whenever pulmonary or tracheobronchial lesions are detected.

MAX PINNER.

DISTURBANCES OF THE WATER BALANCE IN PULMONARY TUBERCULOSIS. R. MEYER-BISCH, Beitr. z. klin. d. Tuberk. **65**:317, 1926.

In tuberculosis, the water balance is frequently disturbed in such a way that both the tissues and the blood contain less water than normal. This condition causes a relative increase in the serum proteins but, independent of

this, there may be a true increase of proteins in the serum. During tuberculin reactions, the water balance is frequently disturbed in the opposite direction. It is possible that the judicious use of tuberculin may therefore correct the dehydration in tuberculosis.

MAX PINNER.

THE TREATMENT OF COCCIDIOSIS. I. COCCIDIOSIS OF THE RABBIT. B. J. KRIJGSMAN, Centralbl. f. Bakteriöl. **101**:108, 1927.

Krijgsmann states that in the case of coccidiosis of rabbits most of the fatal cases result from sepsis due to the intestinal lesions. He found atoxyl of no value in curing the condition, but creolin given in $\frac{1}{4}$ per cent solution by stomach tube, 20 cc. per kilogram, was of great value in curing the disease.

PAUL R. CANNON.

BACTERIOLOGIC INVESTIGATION OF A PARATYPHOID EPIDEMIC. KIKUO SAKAI, Centralbl. f. Bakteriöl. **101**:193, 1927.

Sakai describes a paratyphoid epidemic which occurred in the Normal School at Sendai in 1922. From October 11 to 26, 77 of 223 persons became ill. Agglutination tests, examination of the stools and blood cultures all proved the epidemic organism to be a *B. paratyphosus* B. strain.

PAUL R. CANNON.

PARASITES OF THE TYPE SERGENTELLA. G. I. PÉRÈKROPOFF, Centralbl. f. Bakteriöl. **101**:229, 1927.

Pérèkropoff describes a parasite found in the blood of a young woman, which appears to belong to the group *Sergentella*.

PAUL R. CANNON.

A FUNGUS ISOLATED FROM THE TONGUE. "PENICILLIUM LINGUAE" (GENRE SCOPULARIOPSIS). ANGELIQUE PANAYOTATOU, Centralbl. f. Bakteriöl. **101**:231, 1927.

The author describes a fungus isolated from the brownish growth on the tongue of a child, aged 2. The cultural, morphologic and pathogenic properties are described and as it appears to be a species hitherto undescribed, it is called *Penicillium linguae* (genre *Scopulariopsis*).

PAUL R. CANNON.

THE USE OF ISOPROPHYLALCOHOL AS A DISINFECTANT IN PLACE OF ETHYL ALCOHOL. HEINZ SPRANGER, Centralbl. f. Bakteriöl. **101**:236, 1927.

Spranger found isopropyl alcohol to be as good and in some cases better as a disinfecting agent in places than when ethyl alcohol is used.

PAUL R. CANNON.

CONJUNCTIVAL GRANULOMA DUE TO RHINOSPORIDIUM. N. ORLANDI. Virchow's Arch. f. path. Anat. **262**:314, 1926.

A case of granuloma of the conjunctiva due to *Rhinosporidium seeberi* is reported by Orlandi as the first European example of infection by this parasite. The lesion occurred in a native Italian woman, aged 56 years. The eye had been injured by a splinter of wood, and a small granuloma developed slowly and without pain or disturbance of vision in the area of the conjunctiva which had been contused by the injury. Two removals were followed by recurrences.

The subepithelial tissue was the seat of a granulomatous reaction with a rich lymphocytic infiltration. In the inflammatory tissue were the characteristic organisms. The smallest stages seen, which were oval, mononucleated bodies, from 6 to 9 microns in diameter, already had a refractile capsule. When the parasite reached a size of from 40 to 60 microns, repeated nuclear divisions to the number of fourteen occurred. At the end of the divisional process the parasite had reached a size of from 120 to 140 microns, the mass of spores being surrounded by a dense hyaline capsule which are the reactions of cellulose. Dehiscence of the capsule occurred at a pore, the spores being emptied and the shrunken capsule remaining. Seeber apparently reported the first case from Buenos Aires in 1900. He and some of those who followed him considered the parasite a sporozoon, the name *Coccidium seeberi* being proposed in 1903. In the same year, Minchin and Fantham proposed the name *Rhinosporidium kinealyi*. Ashton of Edinburgh in 1923 was able to show that the organism is not a protozoon but a plant parasite belonging to the phycomycetes; he proposed the name *Rhinosporidium seeberi*. It has not been possible to grow the organism on artificial mediums nor to transmit it to lower animals. Most of the infections by the parasite have occurred in India and have been characterized by polypoid granulations of the nose or pharynx. According to Orlandi, his is the seventh reported example of conjunctival infection. Other still rarer localizations have been the lacrimal gland, the uvula, a papilloma of the penis, and a polyp of the external auditory canal.

O. T. SCHULTZ.

STREPTOCOCCUS INFECTION OF THE RETICULO-ENDOTHELIAL SYSTEM: ITS RELATIONSHIPS AND THE ABILITY OF THERAPY TO INFLUENCE IT. N. LOUROS AND H. E. SCHEYER, *Ztschr. f. d. ges. exper. Med.* 52:291, 1926.

A series of sixty-nine white mice were infected with eighteen different strains of streptococci, either intravenously or intraperitoneally. Some animals died within a few hours, others in a few days and others were killed. At autopsy, some reaction was found in all organs containing reticulo-endothelium, but often one organ was involved to a greater extent than the others.

The characteristic changes in the liver included: (1) A deep staining of the nuclei of the Kupffer cells with Pappenheim's stain; (2) hypertrophy of the Kupffer cells with a projection and breaking off of these into the capillary lumen; phagocytosis of erythrocytes, broken up leukocytes and bacteria by the Kupffer cells; (3) hyperplasia of Kupffer cells forming small foci usually of from ten to twenty cells but sometimes of several hundred. This reaction was perivascular, arising from the adventitia. (4) Often small foci of necrosis of adjacent liver cells which never suppurred nor appeared to contain thrombi or bacterial emboli.

In the spleen the typical appearance include: (1) Proliferation in the "outer zones" separating germinal centers from the pulp; (2) the appearance of "reaction centers" within the germinal centers in which the central reticulo-endothelial cells were enlarged and proliferating and there was phagocytosis of erythrocytes, bacteria and lipoid. Giant cells of two types were encountered, large cells with light staining protoplasm and pale, clear nuclei (Pappenheim's stain); and large cells with lilac or rose colored protoplasm and irregular nuclei—a degeneration form of the first type. Foci of necrosis were encountered, arising chiefly in the outer zones of the follicles.

To determine the effect on animals of damaging the reticulo-endothelial system prior to infection, a group of mice were injected with trypan blue in doses of from 0.3 to 1.0 cc. It was found that animals treated with trypan, then infected

with the streptococci, died more quickly than controls treated only with trypan or only with streptococci. Animals first infected, then treated with trypan died sooner than the controls described, but later than those in which the order of injection was reversed. Analogous results were obtained using elektroferrol instead of trypan blue.

The injurious effects of the trypan and the iron preparation were apparent. The authors consider the injury due to a chemical poisoning of the reticulo-endothelial cells rather than to a mechanical "blockade," because after the trypan and iron injections the reticulo-endothelial cells for the most part showed undiminished phagocytic ability, and in some of the animals dying spontaneously no storage of these preparations in the Kupffer cells, etc., was found.

The ability of the reticulo-endothelial cells to store one substance such as trypan blue is not a reliable guide in measuring their entire function.

P. S. RHODES.

BACTERIOLOGIC OBSERVATIONS AT AUTOPSY ON TWO CHRONIC TYPHOID BACILLI CARRIERS. GRONINGER, *Ztschr. f. Hyg. u. Infektionskrankh.* **107**:157, 1927.

In the first case typhoid bacilli were found at autopsy in the bile, in a gallstone, in the wall of the gallbladder, in the liver, and in the contents of the duodenum. In the second carrier, no bacilli had been discovered in the stools during the last two years of the patient's life in spite of frequent examinations, and none were found at autopsy in spite of a careful bacteriologic examination.

W. OPHÜLS.

Immunology

LOCAL AND CONTRALATERAL PASSIVE TRANSFER OF HYPERSENSITIVENESS. LESLIE N. GAY and ELIZABETH CHANT, *Bull. Johns Hopkins Hosp.* **40**:270, 1927.

The experiments were made with the serum of patients with "timothy" hay-fever. The sensitizing power of the serum (0.1 cc. intradermally on the anterior surface of the forearm of a normal person) did not parallel the severity of the disease as indicated by the reaction to 0.05 cc. of diluted timothy extract intradermally. Heating the serum to 56 C. for half an hour reduced the sensitizing power. The reactive power of the sensitized area diminished gradually. Injecting sensitive serum and timothy extract caused striking reactions. A normal person was sensitized, and concentrated timothy extract was injected on the opposite side: in from twenty-two minutes to two hours reactions developed about the sensitized points—contralateral passive transfer.

KAHN AND WASSERMANN TESTS. T. G. HULL, *J. A. M. A.* **88**:1865, 1927.

Relative agreement was obtained in 97.8 per cent of 25,744 specimens. The advantages of the Kahn test are saving in time, labor and cost, simplicity, reduction of technical errors and good "reactions in specimens in which the Wassermann is anticomplementary."

A STUDY OF PNEUMOCOCCI ISOLATED FROM HORSES UNDERGOING PNEUMOCOCCUS IMMUNIZATION. AUGUSTUS B. WADSWORTH and G. M. SICKLES, *J. Exper. Med.* **45**:787, 1927.

It has been shown that the pneumococcus multiplying in the tissues of the immunized animal (horse) becomes attenuated; it loses, in varying degrees, its virulence, capacity of capsule formation, susceptibility (?) to phagocytosis, and

type specificity. The antigenic activity as an immunizing agent and the production of "soluble specific substance" are also altered. In some instances, the typical pneumococcus characteristics may be quickly restored by one or two passages through a susceptible animal (mouse). In others, virulence is not recovered and the organism remains atypical.

Whether these changes are to be attributed to the specific action of immune bodies in the tissues, or are to be considered as the result of some biologic adaptive process to an adverse environment, has not been determined. Proof of the specific action of immune bodies is possibly open to question, whereas it is well known that virulence and with it some other characteristics are profoundly effected under unfavorable conditions in the absence of immune bodies, notably when the organism is grown at elevated temperatures or in certain unsuitable mediums.

These studies of pneumococci isolated from the infected immunized horse provide opportunities for further investigation of the significance of changes in virulence, type specificity, and formation of "soluble specific substances" in various forms of pneumococcus infection.

AUTHORS' SUMMARY.

BLOOD GROUPING OF POLAR ESKIMO. PETER HEINBECKER and RUTH H. PAULI, *J. Immunol.* **13**:279, 1927.

Of the Eskimos studied, 80.65 fell into group A (Jansky), and those falling into other groups were shown to be mostly half-breeds. The pure Polar Eskimo belongs to group A.

INFLUENCE OF AGE ON SKIN SENSITIVENESS OF TUBERCULOUS GUINEA-PIGS. J. FREUND, *J. Immunol.* **13**:285, 1927.

Young tuberculous guinea-pigs give slight if any reaction to intradermal injection of watery extract of tubercle bacilli, while adult pigs under the same conditions present redness, edema and necrosis at the site of injection.

ABSORPTION OF TOXIC SUBSTANCE OF NORMAL GOAT SERUM BY GUINEA-PIG TISSUE. JOSEPH D. ARONSON, *J. Immunol.* **13**:289, 1927.

Goat serum lyses guinea-pig corpuscles and causes necrosis when injected subcutaneously or intradermally and death when injected intraperitoneally or intravenously in guinea-pigs. Liver, kidney, skin, testes and corpuscles of guinea-pigs absorb the hemolytic, necrotizing and toxic substance, but not after being heated at 70 C. for thirty minutes.

BACTERIOPHAGE. ANTIBACTERIOPHAGE REACTION: BACTERIOPHAGE PURIFIED WITH LIPOIDS. EMIL WEISS, *J. Immunol.* **13**:301 and 311, 1927.

Bacteriophage is not destroyed by union with antiserum, but becomes active again after the mixture is digested with trypsin. Bacterial proteins in a phage fluid can be precipitated by lipoids, and the phage in that way is greatly purified.

THE ISOLATION, PURIFICATION AND CHEMICAL NATURE OF IMMUNE HEMOLYSINS. SUSUMA UCHIDA, *J. Infect. Dis.* **40**:588, 1927.

A slight degree of dissociation of immune hemolysin from sensitized sheep and human erythrocytes was found to occur in 10 per cent solution of saccharose and 5.6 per cent solution of dextrose in the first extraction, with additional but smaller amounts of dissociation in repeated extractions. While both the amount and the temperature of the dissociating fluid influence the degree of dissociation

of the immune hemolysins, neither the period of dissociation nor a solution of weakly alkaline reaction produces any appreciable effect.

To obtain a more nearly pure hemolysin, the broken up erythrocytes, lipoids and sodium chloride were removed from the sugar solution by extraction with pure ether and dialysis, and the saccharose by dialysis and the salting out method. The immune hemolysins being insoluble in ether and not affected by it, indicate that they are not lipoidal. The failure of the isolated immune hemolysins to dialyze through parchment suggests their colloidal nature.

THE ISOLATION, PURIFICATION AND CHEMICAL NATURE OF TYPHOID ANTIBODIES.
SUSUMA UCHIDA, *J. Infect. Dis.* **40**:597, 1927.

In the isolation of typhoid agglutinin and complement-fixing antibody from the sensitized organisms, best results were obtained with a 10 per cent solution of saccharose. Dissociation of both antibodies in saccharose solution occurred best at 60 C. for from twenty to thirty minutes. The addition of sodium hydroxide to the saccharose solution increased the degree of dissociation of both agglutinin and complement-fixing antibody; the addition of hydrochloric acid reduced the degree of dissociation.

By means of a "salting out" method, dialysis and concentration of dialysate, final solutions containing agglutinin and complement-fixing antibodies were obtained free from sugar and salt by containing about 4.8 to 8.4 mg. of total nitrogen per hundred cubic centimeters and a doubtful minute trace of protein.

SERUM ANTILYSINS AND METHODS FOR THEIR REMOVAL. SUSUMA UCHIDA,
J. Infect. Dis. **40**:605, 1927.

Bacteria and their products, the products of hemolyzed erythrocytes, and bile are strongly anticomplementary, while urea, creatinine, creatine, glucose and bilirubin are but feebly anticomplementary. Uric acid and cholesterol are more anticomplementary and occurring in human serums in excessive amounts may render them anticomplementary. All are more anticomplementary in the presence of Wassermann antigen.

Adsorption of anticomplementary serums with kaolin, blood charcoal, infusorial earth, barium sulphate and corpuscles is not of practical value in relation to complement-fixation tests.

Changes in the hydrogen ion concentration of anticomplementary serums were without appreciable influence on thermostable antilysins.

REMOVAL OF ANTICOMPLEMENTARY SUBSTANCES WITH HYDROCHLORIC ACID (SACHS' METHOD). SUSUMA UCHIDA, *J. Infect. Dis.* **40**:610, 1927.

The Sachs' method of testing anticomplementary serums completely removed the thermostable antilysins from about 55 per cent of the serums and reduced their amounts in the remaining 45 per cent, and also removed some of the Wassermann antibody in all of the syphilitic serums tested.

This method has been found of practical value in the Wassermann tests of slightly anticomplementary serums which contain large amounts of antibody.

INFLUENCE OF ANTICOMPLEMENTARY SUBSTANCES ON WASSERMANN ANTIBODY.
SUSUMA UCHIDA, *J. Infect. Dis.* **40**:615, 1927.

The Wassermann antibody in the serums and spinal fluids of syphilitic persons is highly resistant to the thermolabile and thermostable antilysins developed under varying conditions.

SKIN REACTIONS WITH PNEUMOCOCCAL AND OTHER BACTERIAL FILTRATES AND EXTRACTS. RUSSELL D. HERROLD and EUGENE F. TRAUT, J. Infect. Dis. **40**:619, 1927.

It may be concluded, at least tentatively, that the gonococcus, meningococcus, typhoid bacillus, pyocyaneus bacillus, *Staphylococcus aureus* (furunculosis) and colon bacilli of renal infections when grown in broth produce substances which act on the skin in such a manner as to merit further study. More accurate titration of the skin test unit of filtrates of streptococci from chronic prostatitis might give results of some value.

There is a distinct difference between the skin reactions of patients with pneumonia and those of other persons to the filtrates and extracts of the pneumococcus. The majority of patients with pneumonia do not give any reactions, and the majority of normal persons give positive reactions. The condition preventing a reaction develops early in pneumonia and usually persists throughout convalescence.

No specific relationship has appeared between the skin reactions in the various types of pneumonia as classified by type agglutinating serums, and the type of pneumococcus used in the preparation of the filtrate or extract.

The results of neutralizing and protective experiments indicate that the failure of skin reaction depends on specific antibodies that have developed in response to the disease. Whether pneumococcal filtrates are more specific than extracts in physiologic sodium chloride solution will have to be determined by comparison in a larger series, but for strains which have been cultivated on artificial medium for a long time the filtrates seem more specific.

AUTHORS' SUMMARY.

SPECIFIC SKIN AND TESTIS REACTIONS WITH CULTURE FILTRATES OF COCCIDIOIDES IMMITIS. EDWIN F. HIRSCH and HARRIET BENSON, J. Infect. Dis. **40**:629, 1927.

The results obtained indicate that the growth of *coccidioides immitis* in liquid mediums liberates a soluble specific substance which in animals infected with *coccidioides immitis* and in patients with coccidioidal granuloma causes skin reactions like those occurring with tuberculin in tuberculous animals. The immediate skin reaction resembles the wheal produced by the specific pollen extract in a patient with hay-fever. This soluble specific substance is not destroyed by heating to 80 C. for thirty minutes. The reactions with the filtrate of a synthetic medium culture are like those obtained with filtrates of ordinary broth cultures. Prolonged electrodialysis of the synthetic medium filtrate causes the separation of white floccules. These dissolve readily in distilled water containing a few drops of hundredth normal sodium hydroxide, and the solutions cause skin reactions like those of the original filtrate. Not all of the specific substance is flocculated by electrodialysis.

The intratesticular injection of liquid culture filtrates causes a gross reaction in guinea-pigs with coccidioidal granuloma like that in the testes of tuberculous animals after injections of tuberculin.

THE SPECIFIC SUBSTANCE OF COCCIDIOIDES IMMITIS. EDWIN F. HIRSCH and DOROTHY D'ANDREA, J. Infect. Dis. **40**:634, 1927.

From a synthetic, protein-free, culture filtrate of *coccidioides immitis*, a specific substance containing nitrogen and carbohydrate is recovered, which in high dilution causes skin reactions in a patient with coccidioidal granuloma.

Similar preparations have been recovered from broth culture filtrates. The dried specific substance is a white powder readily soluble in water, 0.9 per cent sodium chloride solution, dilute alkalis and acids, contains about 3 to 4 per cent nitrogen and, on hydrolysis, from 20 to 40 per cent reducing sugar measured as dextrose. The osazone prepared from a hydrolyzed solution resembles in structure the dextrosazone.

SENSITIZATION OF GUINEA-PIGS WITH BROTH CULTURE FILTRATES AND WITH THE KILLED MYCELIUM OF COCCIDIODES IMMITIS. EDWIN F. HIRSCH and DOROTHY D'ANDREA, *J. Infect. Dis.* **40**:638, 1927.

It is possible, according to the results of these experiments, to sensitize guinea-pigs with broth culture filtrates of *coccidioides immitis* and with the killed, dried mycelium of the mold. In such sensitized animals, immediate and delayed skin reactions are produced by filtrates of the same strain and of other strains of the mold, as well as with solutions of the soluble specific substance obtained from broth culture filtrates. These results are like those obtained by sensitizing guinea-pigs to tuberculin O. T., with injections of either old tuberculin or killed tubercle bacilli.

SPECIFICNESS IN THE PRECIPITIN REACTION OF THYROGLOBULIN. LUDVIG HEKTOEN, HERBERT FOX and KAMIL SCHULHOF, *J. Infect. Dis.* **40**:641, 1927.

Mammalian thyroglobulins are more or less closely related in precipitinogenic properties. Whether specific and common antigens occur in mammalian thyroglobulins, prepared according to Ostwald's method, remains an open question. Apparently there is no antigenic relation between the mammalian thyroglobulins that have been studied and the thyroglobulin of the domestic fowl.

THE PREPARATION AND PRECIPITIN REACTIONS OF EGG ALBUMIN AND BLOOD PROTEINS OF THE DOMESTIC FOWL. LUDVIG HEKTOEN and ARTHUR G. COLE, *J. Infect. Dis.* **40**:647, 1927.

According to the precipitin reaction, albumin can be separated from the other principal proteins of chicken blood plasma by ammonium sulphate precipitation and dialysis, but it seems that this method is incapable of bringing about a complete separation of euglobulin and pseudoglobulin. It is difficult also, if not impossible, to secure in this way a complete separation of fibrinogen from euglobulin.

There is a definite immunologic relationship between the albumins of egg white and of chicken blood and the albumin of egg white may be resolved into several fractions which differ widely in their reactions with precipitin serum for blood albumin.

INFLUENCE OF COAGULATION ON BACTERICIDAL POWER OF BLOOD. V. G. WALSH and D. HARMSWORTH, *Brit. J. Exper. Path.* **8**:135, 1927.

Bactericidal properties develop in the early stages of clotting and result in the formation of thrombin.

IMMUNITY IN EXPERIMENTAL HERPES. S. P. BEDSON and G. J. CRAWFORD, *Brit. J. Exper. Path.* **8**:138, 1927.

Immunity develops on recovery from infection in guinea-pigs and following hyperimmunization, the serum conferring a degree of passive immunity.

EXPERIMENTAL PNEUMOCOCCAL SEPTICEMIA AND ANTI-PNEUMOCOCCAL IMMUNITY.

HEDLEY D. WRIGHT, J. Path. & Bact. **30**:185, 1927.

Virulent pneumococci inoculated into a normal rabbit undergo rapid removal for a short period but subsequently increase in numbers. Avirulent pneumococci are removed more rapidly and do not reappear in the blood. Immunization enhanced the capacity of the animal to remove virulent organisms and prevents their reappearance. This improvement can be detected to a slight extent five hours after injection of killed culture and becomes marked three days thereafter. It has been observed to last as long as ten months after immunization. It is type specific. The outstanding effect of immunization with type I pneumococci is the enhancement of activity of the body fluids favoring phagocytosis, but the existence of a slight residual purely cellular immunity cannot be altogether excluded. Agglutinins, opsonins, precipitins and complement fixing antibodies do not appear to be essential as such to this improvement. The blood of a normal rabbit is bactericidal to avirulent pneumococci or inhibits their growth. It has no such action on virulent pneumococci. Blood of an immunized rabbit is destructive to virulent pneumococci or delays their growth. The property of delaying the commencement of growth appears earlier and lasts far longer than any other antibody activity tested. The destructive action of the blood is of a much lower order than that of the animal as a whole. The leukocytes may be considerably reduced without interfering with the capacity of the animal to dispose of organisms introduced into the blood. "Blocking" of the reticulo-endothelial system has proved similarly ineffective. This is thought to be due to the complexity of the clearing mechanism involving, as it does, a variety of phenomena of adhesion and phagocytosis by mutually complementary systems of cells. Virulent pneumococci injected in the phase of latency behave in vivo as in vitro. The increase occurring some time after injection is due to their passing into the phase of active growth. Virulent pneumococci introduced in the active phase of growth do not undergo the preliminary rapid removal.

AUTHOR'S SUMMARY.

A NEW METHOD OF PREPARING STAPHYLOCOCCAL HEMOLYSIN. JOSEPH W. BIGGER, J. Path. & Bact. **30**:271, 1927.

A new method of preparing staphylococcal hemolysin is described. It consists in suspending staphylococci from a solid medium in saline solution and freeing the fluid from cocci by centrifugalizing. The lysin so prepared is purer than any previously described, since it is free from the various adventitious substances present in broth cultures. It has a high titer, and a minimum hemolytic dose of 0.000007 cc. for sheep cells has been recorded when the total volume in each tube was 2.0 cc. and the amount of cell suspension present similar to that used in the Wassermann test.

The lysin acts on sheep cells and human cells, but better on the former than on the latter. It acts at cold-room, air and body temperatures, and the highest titers are obtained by incubation at 37 C., followed by exposure to air or cold-room temperature. Twenty-four strains of *Staphylococcus aureus* were tested, and sixteen of these were found to produce this lysin. In some instances an organism freshly isolated did not, and after a few subcultures did, produce the lysin. This lysin is probably identical with the lysin produced in broth cultures. By using this lysin, hemolysis in blood agar plates has been produced, identical with that produced by a colony of a hemolytic *Staphylococcus aureus*. The lysin is very thermostable, the titer being reduced only to about one-half by an exposure to 100 C. for half an hour. The lysin can be obtained

in dry form by evaporation and remains unaltered in activity in this condition for months. The lysin acts best in a medium with a slightly alkaline reaction. It has not been found possible to produce a definite antibody to this lysin.

AUTHOR'S SUMMARY.

PHENOL AND TRICRESOL EFFECTS IN TOXIN AND ANTITOXIN SOLUTIONS. C. G. POPE, *J. Path. & Bact.* **30**:301, 1927.

A separation of phenol can be shown to occur when a 0.5 per cent phenol solution is frozen. The extent of the separation of phenol depends on the protein and salt content of the toxin or antitoxin solutions, the freezing temperature and the duration of freezing. When these factors permit, a critical amount of phenol may separate from a toxin-antitoxin mixture, causing a greater relative destruction of antitoxin than of toxin and rendering the mixture toxic. A separation of phenol can be shown to occur at the air liquid interface when a 0.5 per cent solution of phenol in water or toxin is shaken. This separation of phenol causes marked destruction of the specific substances when dilute solutions of toxin or antitoxin containing these antiseptics are shaken in a partially filled bottle. The use of phenol or tricresol in material for the Schick test or for the Schultz-Charlton test is therefore inadvisable.

AUTHOR'S SUMMARY.

THE EFFECT OF HEAT ON THE AGGLUTINATION OF BACTERIAL EMULSIONS. AMAR NATH GOYLE, *J. Path. & Bact.* **30**:331, 1927.

Normal strains of *B. typhosus* and *B. enteritidis* (Gaertner) have been shown to contain two kinds of antigen, one of which is heat labile and the other heat stable. By heating to 100 C. for thirty minutes the former is rendered inagglutinable by specific serum, while the latter is not affected. A number of strains of *B. typhosus* and *B. enteritidis* have been made to yield two forms (N and R) by plating old broth cultures. The colonies of the R form on agar differ from those from the N form in being larger and in having a surface that is markedly granular. The S form has been obtained by growing the N form on agar containing 0.1 per cent carbolic acid but not as a permanent variant. The N, S and R forms differ in their antigenic, absorbing and agglutinating properties. The R forms have been shown to possess a peculiar type of antigen which is common to the R forms of *B. typhosus* and *B. enteritidis*. Some N forms may contain in addition to the normal specific heat-stable antigen a variable quantity of another heat-stable antigen which is nonspecific, but which is distinct from the nonspecific antigen peculiar to the R form. It is the possession of this nonspecific heat-stable antigen in the N strains and the R antigen of *B. typhosus* and *B. enteritidis* that accounts for the old observation of the phenomenon of cross-agglutination between these species. The diminished agglutinability of a heated bacterial emulsion appears to depend on the destruction of the heat-labile portion of the antigen of the bacteria. The following additional conclusions follow from the experiments detailed and the observations cited in this paper. The antigen that is peculiar to the R form and is held in common by the R variant of *B. typhosus* and *B. enteritidis* is heat stable, i. e., resists a temperature of 100 C. for thirty minutes, and replaces the heat-stable or O antigen. An explanation of the presence of agglutinins for *B. coli*, *B. enteritidis*, etc., in the blood of patients having typhoid fever and normal adults has been suggested.

AUTHOR'S SUMMARY.

VARIATION IN GLYCEMIA IN ANAPHYLACTIC, HISTAMINE AND PEPTONE SHOCK.
J. LABARRE, Arch. internat. de méd. exper. 3:41, 1927.

This is an experimental study chiefly of guinea-pigs, but also of rabbits and dogs to determine the cause of variations in blood sugar in shock. The blood was withdrawn from the animal while in shock at intervals of twenty or thirty seconds for two or three minutes. In anaphylactic shock, caused by injecting horse serum into guinea-pigs, and in histamine and peptone shock, a sudden rise in blood sugar occurred which reached its maximum one minute after the injection and generally fell below the level in a control animal at the end of two minutes. The rise was somewhat higher and more abrupt in histamine shock than in peptone shock. A marked hypoglycemia followed in severe shock, whereas no change occurred in feeble shock. The rise was coincident with the convulsions. Asphyxia probably was not the cause, because in asphyxia hyperglycemia is later in onset and may occur in shock without asphyxia. Yet in both conditions, i. e., shock and asphyxia, a hyperadrenalinemia occurs. This was not true in anaphylactic shock.

Anaphylactic shock in the dog was not accompanied by hyperadrenalinemia. Histamine and peptone caused a rise in the secretion of epinephrine which started immediately after the injection and was of short duration. Hyperglycemia occurred in adrenalectomized animals.

After paralysis of the sympathetic nerve by ergot, the blood sugar rose when shock was produced, but the values were lower than in control animals.

Excitation of the peripheral end of the vagus caused a slight elevation of sugar which could be prevented by previous injection of atropine. After administration of the atropine, hyperglycemia did not occur when shock was produced. Section of both vagi caused a diminution in the hyperglycemia of shock. After ligation of the portal vein hyperglycemia of shock did not occur; if anything, a slight hypoglycemia followed. A marked fall in the glycogen of the liver occurred coincident with the hyperglycemia of shock. This was more marked in anaphylactic and histamine shock than in peptone shock. In inanition, shock did not cause a hyperglycemia because the glycogen of the liver was exhausted.

Hyperglycemia of shock is not under central control, nor is it due to the action of the sympathetic system or to the activity of the suprarenals. The evidence points to vagal control, and that peripheral, because it occurs in decerebrate animals and after section of the vagi in the neck. Peripheral stimulation of the vagus causes a liberation of glucose from the liver to replace the sudden arrest of glycolysis in the blood. The elevation of blood sugar at the height of shock is accompanied by an increase in the blood lactic acid.

N. ENZER.

EXPERIMENTAL CONGENITAL CATARACT. A. BAIVY, Arch. internat. de méd. exper. 3:60, 1927.

The author presents the results of his experiments to test the work of Guyer and Smith on the production of congenital cataract, by injecting the gravid animal with anticrystallin prepared in the cock. Thirty young rabbits were obtained from six gravid ones thus treated. Two had opacity of the lens, which disappeared in a few days. Eight had small, weak eyes. One presented at autopsy a soft liquefied lens, and one a definite cataract. No changes in the eyes occurred in the controls.

Baivy is undecided as to the mechanism—whether it is a precipitation in utero of the crystallin of the fetus by an anticrystallin in the blood of the mother or whether, as Guyer and Smith believe, it is due to a destruction of

the lens by cytolysins which accompany the precipitin prepared by the cock. Why it attacks the fetus and not the mother may be due to the fact that the lens of the fetus is more exposed to the blood stream in the hyaloid artery, which is not present in the adult.

A practical suggestion is made, namely, that it is inadvisable to operate for cataract in a pregnant woman because of the large amount of anticrystallin which might develop, as may occur after simple incision of the lens in rabbits.

N. ENZER.

PHYSICOCHEMICAL PROCESSES IN ISO-AGGLUTINATION. V. SCHRÖDER, Arch. f. d. ges. Physiol. **215**:32, 1926.

Iso-agglutination is accompanied by a decrease in the electric charge of the erythrocytes. The same phenomenon was observed in acid agglutination. The ratio between albumin and globulin was found by nephelometry to be the same in the four blood groups.

THE EPIDEMIOLOGIC AND CLINICAL SIGNIFICANCE OF THE COMPLEMENT FIXATION REACTION IN RHINOSCLEROMA. B. ELBERT, B. FELDMAN and W. GERKES, Centralbl. f. Bakt. **101**:384, 1927.

The complement-fixation reaction, *B. rhinoscleromatis* being used as the antigen, is of great value in the diagnosis of rhinoscleroma, not only in the active, but also in the latent, forms.

PAUL R. CANNON.

THE THROMBOZYTOTARINE AGAINST AMOEBA ENDOLIMAX AND LEISHMANIA TROPICA. R. E. MESSIK, Centralbl. f. Bakt. **101**:413, 1927.

Messik has studied the Rieckenberg phenomenon as to specific antibodies which cause the blood platelet agglomerating effect with *Endameba tropica*. Several injections of mice with amebae did not form any thrombozytobarine, but in the case of *Leishmania tropica*, thrombozytobarine was formed and the platelet covering effect occurred and persisted for several months. The effect was not transmissible from mother to child.

PAUL R. CANNON.

ALCOHOLIC EXTRACTS OF BACTERIA AS ANTIGENS. A. KLOPSTOCK and E. WITEBSKY, Klin. Wchnschr. **6**:119, 1927; A. KLOPSTOCK, Ibid., p. 120.

When rabbits were injected with alcoholic extracts of *Proteus X 19* and tubercle bacilli, antiserums were obtained that, while in some degree specific, reacted with various lipoids. It is suggested that the extracts may have contained some alcohol-soluble protein beside lipid material. On injection of alcoholic extracts of horse kidney and of *Proteus X 19* so-called heterogenetic antibody appeared in the serum.

THE ANTIGENIC FUNCTION OF ALCOHOL-SOLUBLE SUBSTANCES OF HUMAN BLOOD CELLS OF DIFFERENT GROUPS. E. WITEBSKY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **48**:369, 1926.

The author reports experiments in which lipid antiserums were prepared by the injection of rabbits with the alcohol extract of human red cells of each of groups I, II and III combined with guinea-pig serum. The lipid antiserum, so prepared, with group I cells had neither an agglutinating nor a hemolytic action on human red cells. Such serum caused complement fixation with alcoholic extracts from human blood, but showed no group specificity. Lipid anti-

serums obtained in the same way with cells of group II had an agglutinating and a hemolyzing action on human cells of group II; in complement-fixation tests, these group II antisera had an elective action on alcoholic extracts from bloods of group II. Antiserum prepared with cells of group III had no agglutinating or hemolyzing action on red cells of any group; in complement-fixation tests, these group III antisera reacted more strongly with alcoholic extracts from group III bloods than with those from groups I and II. These serums, however, showed a considerable amount of nonspecific lipoid antibodies.

PAUL R. CANNON.

AGGLUTINATION REACTIONS WITH AGED ERYTHROCYTES. F. SCHIFF and W. HALBERSTAEDTER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **48**:414, 1926.

The authors describe and discuss an instance in which careful typing of the erythrocytes showed the patient to be in group III. After allowing these erythrocytes to stand for four days, they were then agglutinated by serums of group III and IV. Tests with other patients showed that after the erythrocytes had stood for six or seven days, three of twenty-three showed agglutination with serum from the same blood group. The agglutination was most marked when the blood was kept in the icebox.

PAUL R. CANNON.

THE SPECIFICITY OF THE TUBERCULIN REACTION. M. MASTBAUM, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **48**:428, 1926.

Mastbaum discusses the arguments for and against the claim of specificity in the tuberculin reaction and then tested nine guinea-pigs which reacted negatively to tuberculin by injecting them twice with *B. coli* vaccine. In two or three weeks, intracutaneous tests were made with *B. coli* vaccine and with tuberculin. In five, hypersensitiveness to tuberculin was demonstrated. In two cases of sensitization, the subcutaneous injection of tuberculin caused an inflammation of the old tuberculin and *B. coli* injection papules. It was not possible to discover a marked difference histologically between the *B. coli* and the tuberculin papules.

PAUL R. CANNON.

THE INDEPENDENCE OF LIPOID AND PROTEIN ANTIBODIES IN IMMUNE SERUMS OBTAINED BY COMBINED INJECTION. SIEGFRIED HEINSHEIMER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **48**:438, 1926.

The author's experiments agree with those of Doerr and Hallauer that antisera prepared by the injection of animals with a combination of alcoholic extracts of various antigens and guinea-pig serum contain both protein and lipoid antibodies which can be isolated by absorption procedures with corresponding type antigen. These two types can also be demonstrated by complement-fixation and precipitation tests.

PAUL R. CANNON.

THE THEORY OF COMPLEMENT-FIXATION. L. SILBER and W. TSCHERNOWOSTOW, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **48**:472, 1926.

The authors' experiments indicate that the fixation of complement depends on physical conditions, such as phases of dispersion and adsorption properties rather than on any special properties of antigen or antibody. Complement is bound to the antigen-antibody complex, not because the latter is a specific complex, but because the formation of this complex gives rise to various degrees of dispersity, as manifested by opalescence and flocculation.

PAUL R. CANNON.

THE INFLUENCE OF LIGHT ON TUBERCULIN. W. HAUSMANN, W. NEUMANN and K. SCHUBERTH, *Ztschr. f. Tuberk.* **47**:113, 1927.

Old tuberculin which was rendered inert for skin reactions by radiation with light of short wave length produced in man the same general reactions, such as fever and polyuria, as untreated tuberculin. The use of the radiated tuberculin (ultratubin) is suggested for therapeutic use on patients who are troubled by strong local reactions.

MAX PINNER.

Tumors

INFLUENCE OF LIGHT ON GROWTH AND MALIGNANCY OF TRANSPLANTABLE NEOPLASM OF THE RABBIT. LOUISE PEARCE and WADE M. BROWN, *J. Exper. Med.* **45**:727, 1927.

Experiments are reported in which an environment of constant and continuous light with a wave length of from 3,022 to 5,790 angstrom units, supplied by mercury arcs in crown glass, and of constant darkness, have influenced the course and character of a malignant disease of rabbits induced by a transplantable neoplasm. Under the influence of constant light, the level of malignancy was lower than in control animals living under ordinary conditions of diffused sunlight. Under the influence of constant darkness, the level of malignancy was somewhat lower than in control animals, but the effect of this environment was modified by the special character of the disease prevailing at this time. The incidence of bone metastases was unusually high, but it was greatly increased in rabbits kept in constant darkness. These observations furnish experimental evidence in support of the belief that there is a correlation between external factor of light and the manifestations of an experimental malignant disease.

AUTHORS' SUMMARY.

ANGIOPLASTIC SARCOMA OF TESTICLE. LOUIS SKUBISZEWSKI, *Trav. des Institute d'Anatomie Path des Universités de Pologne* **2**:1, 1927.

The tumor developed in a man, aged 25. The primary tumor of the right testicle consisted of mononuclear cells; in the metastatic growths in the liver were large multinucleated protoplasmic masses arising, it is thought, from the capillary endothelium. The first tumor of the testicle of this kind was described by Malasse, and Monod in 1875.

LIPOMA OF CEREBRAL PIA. JÓSEF LASKOWSKI, *Trav. des Institute d'Anat. Path. des Universités de Pologne* **2**:13, 1927.

The tumor was found arising from the pia of the anterior and inferior surfaces of the frontal lobes in a woman, aged 72. In addition to fat tissue, the tumor contained connective tissue and neuroglia, and was associated with defective development of the callosum.

SYSTEMIC SARCO-ANGIOMA. CONTRIBUTION TO STUDY OF TUMORS OF RETICULO-ENDOTHELIAL SYSTEM. WITOLD GRABOWSKI, *Travaux des Institute d'anat. Path. des Universités de Pologne* **2**:53, 1927.

In a man, aged 32, who died seven months after removal of a greatly enlarged spleen, there was found a peculiar proliferation of the endothelium, with tendency to the formation of cavernous angioma in the spleen, liver, marrow, lymph nodes, suprarenals and kidneys. In the spleen and liver, especially, the endothelial proliferation appeared sarcomatous. The condition is regarded as a disease of the endothelial part of the reticulo-endothelial system.

IS THE SUPRARENAL ORIGIN OF HYPERNEPHROID TUMORS DEMONSTRABLE? LUDWIG PICK, *Med. Klin.* 1:1, 1927.

According to Lubarsch, hypernephroid tumors may simulate suprarenal cortex, or be of two atypical varieties; one in which glandular, cystic or papillary elements occur between typical structures, the other an "atypical anaplastic" form in which the structures in a confused fashion resemble first the suprarenal cortex and then again the kidney, the latter of undetermined histogenesis. Pick regards the suprarenal medulla as a neglected issue in discussions of the origin of such tumors. At the necropsy of a man, aged 44, he found: amyloidosis of the liver, spleen, suprarenal capillaries and arterioles and glomeruli of the kidney; an old healed tuberculosis of the lungs and a mass 9 by 6 cm. in the left kidney, soft with a thin gray-white capsule, extending into the pelvis, divided externally into a distal opaque gray-yellow part and a proximal dark gray-red part, but mottled inside. Microscopically, this had a typical hypernephroid cortex and a center composed of ganglion cells. The tumor was thought to originate in a hypernephrogenous rest in the kidney.

GEORGE RUKSTINAT.

PROGNOSIS IN RADIATED UTERINE CARCINOMA. W. LAHM, *Strahlentherapie* 25:22, 1927.

Basing his conclusions on observations recorded in the literature and personal observations, Lahm discusses the prognosis of radiated uterine carcinoma from a pathologico-anatomic standpoint. Carcinoma of the cervix appears in a number of varieties. Their responses to radiation differ greatly; even in two processes of the same extension, the dose required to cause regression may vary considerably. One can learn from inoculations of healthy animals with cancer how a normal organism reacts to the sudden invasion of malignant cells, but it is extremely difficult to draw any conclusions applicable to human cases from the effect of radiation in such animals. Lahm classifies the zone of reaction between normal and carcinomatous tissue into four groups, depending on the prevalence of plasma cells, eosinophils, mixtures of both, or fibroblasts and fibers. As to spontaneous cure of carcinoma, it is interesting to note that in many cases the invasion of leukocytes followed as a secondary process the necrosis of the tumor cells. No evidence for the assumption that the connective tissue promotes the necrosis of the malignant growth was found. Connective tissue is essential, however, for scar formation. Cornification takes place without assistance of the connective tissue; the frequent observation here of typical cells, called "pencil cells," suggests their importance in this process. As the principal histologic difference between spontaneous change and the change following irradiation, Lahm holds that in the first case, the protoplasm is degenerating while the nucleus remains intact, while in the latter case, the nucleus shows the first signs of injury. The conclusion is that irradiation does not induce a tissue reaction parallel to the one seen in "spontaneous cure." The future development should bring a method that imitates nature's way of healing malignant tumors (*Strauss, Strahlentherapie*: 24:672, 1927).

E. A. POHLE.

EFFECT OF ROENTGEN RAYS ON CARCINOMA. J. BORAK, *Strahlentherapie* 25:105, 1927.

The history of a woman, aged 74, who had a basal cell carcinoma of the left thigh, is related. The growth resembled a cauliflower, was ulcerated, had a bad odor, and was extremely painful. Roentgen-ray therapy was given on

three successive days, 8 Holzknecht units on each day, through 0.3 millimeters of zinc; this corresponds to about 2 skin unit doses. The field was large enough to cover 1 cm. of healthy tissue around the tumor. Shortly after the treatment, the pain lessened; four weeks later, 12 Holzknecht units, through 4.0 aluminum, were administered to the tumor only. No epithelization took place. After six months, the site of the original tumor was still necrotic. Biopsy did not show any carcinoma, and 24 Holzknecht units, through 2.0 aluminum, were given again. Another biopsy three months after this treatment did not reveal any signs of malignancy. As there was no tendency toward healing fifteen months after the beginning of the treatment, grafting was done, which took well. From these observations, the author concludes that following irradiation, two distinctly different processes take place: one, the destruction of the tumor, the other, the formation of scar tissue. It seems that one can appear without the other. For cancer in internal organs, the dose should consequently not be high enough to injure normal tissue.

E. A. POHLE.

SARCOMA IN AN IRRADIATED TUBERCULOUS (?) JOINT. M. BAUMANN, *Strahlentherapie*, **25**:373, 1927.

A woman, aged 23, was treated seven years previously over the right elbow for joint tuberculosis. Following a fall and fracture of the right upper arm directly above the joint, the arm swelled and became painful. The roentgenogram showed a few suspicious spots in the humerus, and operation followed by biopsy established the diagnosis of sarcoma. The author discusses the possibility of a relation between roentgen-ray treatment of the elbow and the development of the sarcoma. No histologic diagnosis of tuberculosis had been made.

E. A. POHLE.

THE DIAGNOSIS OF CARCINOMA BY THE PRECIPITIN TEST. HERMANN LEHMANN-FACIUS, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **48**:397, 1926.

The author describes experiments which indicate the possibility of a diagnosis of carcinoma by a precipitin test, using as antigen a globulin extract of carcinoma tissue. He considers the Abderhalden and the precipitin reaction as depending on the same general principle, only manifesting the reaction in different ways.

PAUL R. CANNON.

THORIUM TREATMENT OF TUMORS. L. HALBERSTAEDTER, *Ztschr. f. Krebsforsch.* **24**:360, 1927.

In place of capillary glass tubes containing radium emanation for the direct radio-active treatment of neoplasms, the author used naked rods of thorium x. To overcome the toxicity of this substance, it was precipitated with barium sulphate. The precipitate was mixed with an indifferent viscous mass, which made it possible to form flexible rods 0.4 mm. in diameter. When the material was so prepared as to have a radio-activity of 0.5 millicuries per centimeter of rod, it was found that pieces 1 cm. in length caused a zone of necrosis 1.5 mm. wide, beyond which was a reaction zone of congestion and lymphocytic infiltration from 4 to 5 mm. wide. The material was introduced in such a way that there was 1 cm. for each cubic centimeter of tissue. Necrosis occurred early and reached its maximum in from three to four days. The material is recommended for tumors that are not too extensive and are superficially situated, such as carcinoma of the lip, tongue, tonsil and nasopharynx, and small carcinomas of the mammary gland.

O. T. SCHULTZ.

Medicolegal Pathology

ANNUAL REPORT FOR 1926 OF COUNTY PHYSICIAN OF ESSEX COUNTY, N. J.
HARRISON S. MARTLAND.

During the year, the county physician of Essex County, which includes Newark, investigated deaths from varying causes as follows: homicidal, 44; suicidal, 96; accidental (highway), 175; falls, 76; abortion, 13; asphyxiation, 61; burns, 38; miscellaneous accidents, 19; accidental poisoning, 30; natural causes, 898. By virtue of a new state law, Essex County recently adopted the medical examiner's system. The report is of interest to students of medicolegal matters.

A CASE OF CYANIDE POISONING. C. D. HOWARD, Boston M. & S. J. **196**:58, 1927.

At least four times the recognized fatal dose of cyanide was taken on an empty stomach by a man, aged 42, but death did not occur until about forty minutes later. The lining of the stomach was brownish red. In the stomach and contents there was the equivalent of 11.8 grains (0.71 Gm.) of cyanide, in the liver one third of a grain (0.02 Gm.), in the kidneys, one tenth of a grain (0.006 Gm.), and in the blood and brain, distinct traces.

IDENTIFICATION BY COMPARISON OF ROENTGENOGRAMS OF NASAL ACCESSORY SINUSES AND MASTOID PROCESSES. WILLIAM L. CULBERT and FREDERICK M. LAW, J. A. M. A. **88**:1634, 1927.

A strange case of identification by roentgenograms of the pneumatic cells of the skull is described, the first of its kind on record. The case establishes a medicolegal precedent. Anthropometric roentgenography may prove to be important for purposes of identification.

EXPERIMENTAL ELECTRIC SHOCK. R. W. S. URQUHART, J. Indust. Hyg. **9**:140, 1927.

Death may be due to primary cardiac or respiratory failure, or to both. In cases in which the current traverses the body from the head to a hind limb, about 45 per cent of the deaths are purely cardiac (in laboratory animals) and the rest respiratory. In such cases and also in those in which the current is passed directly through the brain, a profound blocking is established in the respiratory, vagus and vasomotor centers which fail to respond to stimuli. Definite structural changes may not occur in these centers. The capillary hemorrhages present do not seem to be significant. The blocking may subside and reflexes return under efficient artificial respiration, provided the nerve structures have not been charred. The results emphasize the value in electric shock of artificial respiration, which must be applied early and maintained long enough. The block in the nerve centers is of such nature that ordinary tests for death cannot be relied on except the cooling of the body and the onset of rigor mortis.

MEDICOLEGAL STUDY ON THE SUBMERSION, CARRIAGE AND FLOTATION OF CADAVERS IN WATER COURSES, CANALS, LAKES AND THE OCEAN. P. CHAVIGNY, Strasbourg méd. **84**:393, 1926.

The various conditions that determine the fate of the human body in stagnant and moving waters are discussed, principally on the basis of study of the hydrography of the region of Strasbourg.

FLUORESCENCE AND ITS USE AS A MEANS OF MEDICOLEGAL INVESTIGATION. V. M. PALMIERI, *Rass. internaz. di clin. e. terapia* 7:301, 1926.

The Henry George lamp is recommended for the study of fluorescence. The differences in fluorescence of fresh and old blood spots, of blood pigments and derivatives, especially hematoporphyrin, of diverse other human products and of certain toxic substances are described.

INTRA-UTERINE DECAPITATION WITH UNINJURED GESTATION SAC. B. J. KARDASEWITCH, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:48, 1926.

As a result of obtaining a human embryo with its head torn off in the intact gestation sac in a pregnancy of about 2½ months, which terminated by spontaneous abortion, experiments were made with other human embryos and fetal membranes. When stripes of chorion or amnion were lacerated, little force was found necessary. The smooth thinner part of the chorion was more resistant than the placental portion. These were lacerated with from 22.2 to 174 Gm. of weight. The neck of a human embryo 3.5 cm. long tore with a force of 1.01 Gm. per square millimeter of surface of the estimated minimum cross section; one of 6 cm. with a force 10 Gm. per square millimeter. These amounts were equal to 29 Gm. for the smaller and 582.5 Gm. for the larger embryo, which were in marked contrast to 3,805 Gm. necessary to split open the intact amniotic sac for a human embryo 2.4 cm. long, and the still more remarkable results, 5,038 Gm. for the amniotic sac of an embryo 4.4 cm. long.

The results indicate definitely that severe injuries may be sustained by the fetus at early periods of pregnancy, without damage to the fetal membranes.

E. R. LE COUNT.

UNEXPECTED SUDDEN DEATH DURING PREGNANCY AND LABOR. ERNST ZIEMKE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:129, 1927.

Investigations that explain the unexpected death of women who are pregnant or who were recently pregnant are generally regarded as highly important services. For such undertakings, a prolonged experience is as essential as a thorough comprehension of disease, as is illustrated by this report made last year at the fifteenth annual meeting of the German Society of Legal and Social Medicine in September in Düsseldorf, where the subject was given a prominent place on the program and was well discussed. The report includes a number of Ziemke's most interesting studies during twenty-five years, of causes of both natural and unnatural deaths during or about the time of pregnancy and childbirth, with many observations by others and their opinions concerning similar deaths. For the most part, unusual and obscure conditions are considered, and deaths with which most physicians are familiar, such as postpartum pulmonary embolism, are only casually mentioned. Among those occurring during pregnancy are two due to spontaneous rupture of the aorta. One of the aortas was examined by Katz, who found an earlier rupture which had healed. (A similar healed spontaneous tear with a separate second rupture causing death is reported by Nordlander, *Tr. Chicago Path. Soc.* 12:123, 1925). The rupture in the other aorta studied by Ziemke was due to advanced arteriosclerosis in a woman, aged 22. The hemorrhage into the pericardium began just before labor while she was at stool. She had aborted a few years before, and at the time of death had one greatly shrunken kidney and many scars in the myocardium.

Death from necrosis of the entire cortex of both kidneys during the third month of pregnancy with anuria and two attacks of convulsions attributed to eclampsia, but without any trace of the characteristic eclamptic necroses in the

liver, supplements a few similar reports by others. It may be that such conditions in early pregnancy should now be recognized as a separate disease. Among deaths from natural causes during labor is one from suffocation caused by pressure of the gravid uterus and a mediastinal tumor unrecognized during life. There were also several deaths for which entirely satisfactory explanations were not obtained. Among the latter, mention is made of deaths reported by others of two women who had had syphilis, and two deaths investigated by Ziemke. Reference is not made to microscopic examinations of the brain in connection with any of the four deaths. Presumably they were made, but in discussions as critical as this, the importance of such examinations deserves emphasis, and when they have been made, details of methods employed, the places in the central nervous system studied and what was or was not found should be stated. (See Le Count, E. R., and Singer, H. A.: *The Hazard of Surgical Anesthesia with Syphilis of the Brain*, *Tr. Chicago Path. Soc.* **12**: 105, 1924; *J. A. M. A.* **84**:358 [Jan. 31] 1925.)

The importance of infections as causes for unexpected death after the women are up and around and have apparently recovered from puerperal fever is properly stressed. These are much like the deaths after diphtheria and are accompanied by similar retrogressive processes in the muscle fibers of the heart. Marked dissatisfaction is expressed with the so-called "birth-shock" occasionally employed in the absence of better explanations, for certain deaths during labor. The implication is evident that what has been accepted as shock should possibly be defined more precisely, or receive a new and different explanation. Such an eventuality is as applicable to deaths from shock under other conditions as during childbirth.

The most valuable contribution of this article is in the portion devoted to causes of unnatural death of women, in which shock during attempted abortion is discussed, and in which air embolism successfully replaces shock as a cause for many such deaths. Especially worthy are the accounts of the demonstration of air embolism some hours, or even days, after air was introduced into the uterus with fluids, commonly soapy water, in attempts to provoke abortion, and the views advanced for the delay of embolism to the heart and lungs. That air may pass through the lungs into the systemic arteries and lodge in the coronary arteries and in arteries for important regions in the central nervous system is forcefully advocated. Numerous other particulars in this address by Ziemke should lead to its being carefully and studiously read by all who are engaged in similar investigations.

E. R. LE COUNT.

AN UNUSUAL DEATH FROM SUFFOCATION. A. THEODOROV, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **9**:193, 1927.

The bronchi of both lungs of a man who committed suicide by hanging contained a white substance somewhat molded to the channels, but it did not fill them completely; the trachea and larynx were empty. The white material was found to be a mixture of binitrocellulose and trinitrocellulose, known as Koloxylin, when dissolved in acetic ether. Drinking the solution, as proved by experiments on dogs, caused such an irritation of the pharynx and upper air passages that during spasmodic respirations it was inhaled and solidified in the air passages in the lungs. When the man found that he had not succeeded in poisoning himself with the solution, he resorted to hanging.

E. R. LE COUNT.

IMPRESSIONS OF THE INSTITUTES OF LEGAL MEDICINE IN VIENNA AND PARIS.
J. Fog, Ugesk. f. Laeger. 89:1, 1927. (A translation of the whole article.)

Social conditions within the past few years have emphasized the demands on practical as well as theoretical workers in the field of legal medicine. The development in Denmark has been duplicated in many other countries.

During a sojourn at Vienna in the summer of 1925, and in Paris in the spring of the following year, I had an opportunity to pursue some general studies of institutions devoted to legal medicine and related subjects, and the following results of these observations are submitted as likely to be of general interest.

VIENNA

The school of legal medicine in Vienna was for several centuries, as all medical students know, one of the leading ones in its field. An ordinary professorship of legal medicine was established as early as 1804, the first of its kind within the German-speaking area; simultaneously, a course was offered, terminating with an official examination. It is worthy of notice that so important a subject as pathologic anatomy did not receive the same distinction until many years later; examinations were not offered until 1844. In the same year, lectures on legal medicine were inaugurated for students of jurisprudence. A few years later, an extraordinary professorship in this special field concluded its admittance to academic recognition.

The Institute of Legal Medicine was founded in 1866 in the building which housed also the laboratories of pathologic anatomy and medical chemistry. In spite of repeated expansions during the following years, this arrangement did not remain satisfactory—moreover, the new era which was ushered in by the appointment of von Hoffmann as professor (1875-1897) resulted in a decided increase of initiative and work in every field of activity within the institute.

Von Hoffmann was the founder of the excellent Museum of Forensic Medicine, which, in its field, occupies a dominant position. His textbook of legal medicine became the leading guide to the study of the subject in all civilized countries, and his successors perpetuated this influence by the continued succession of new editions.

After the death of von Hoffmann, in 1897, Haberda assumed his post for one year, whereupon Kolisko, until then professor of pathologic anatomy, actively entered the field of legal medicine. After Kolisko's death, in 1917, Haberda succeeded him as ordinary professor; he had become professor *extraordinarius* in 1898.

At the beginning of the new century the institute developed far beyond its capacity. The World War came, and not until 1922 was Haberda able to open a new, modern institute; this was made possible by a radical remodeling of the so-called Anatomical Building, which until then had been part of the equipment of the First Garrison Hospital.

This institute is located within the center of the town, close by numerous other university buildings and hospitals. Situated at the corner of Sensengasse and Spitalgasse, it adjoins immediately the great Institute of Pathological Anatomy, and across the street is the well known gynecologic and obstetric clinic "Peham."

The Institute of Legal Medicine embraces the following departments: first, a beautiful and roomy amphitheater with seats for 180 persons, a table for postmortem examinations and an excellent projection apparatus; further, two anatomy rooms, each equipped with two tables, separated by a movable glass

partition; finally, an excellent museum, well housed, containing a collection of preparations assembled by the cumulative effort of several generations.

The library is spacious and well equipped. A hall is devoted to the examination of patients referred to the institute by the police. The remainder of the buildings includes the archives room, the secretary's office, the reception room and private office of the chief officer and isolated work rooms for each of the five medical officers attached to the institution. The first floor contains twelve cells for the accommodation of bodies of adults, and some smaller ones for those of children. The temperature within these cells is kept at $+2^{\circ}\text{C}$., but may be lowered according to necessity. In front of the buildings is a small garden.

Although the social conditions in Vienna have been measurably reduced since the war—the new state of Austria includes only 6,000,000 inhabitants—the daily work of the institute continues to bear the stamp of the gigantic city. With its 2,000,000 inhabitants and its cosmopolitan character, complicated by vast districts inhabited by the poor, the city makes great demands on the institute, especially in regard to large volumes of routine work.

The postmortem investigations carried out at the institute are divided into two groups: "gerichtlich-medizinische" (pertaining to legal medicine) and "sanitäts-polizeiliche" (pertaining to the sanitary police). The distinction between these two groups (which, in Denmark, is not recognized, at least not officially) is practical. In the first kind, legal in the strict sense of this term, the procedure is elaborate, the same as it is in Denmark, with a detailed report of the results. In the other group, on the contrary, are minor cases which do not afford any real criminal interest, but rather fall within the sphere of social medicine, and are sufficiently elucidated by investigations which do not go into the detail necessary in typical legal postmortem examinations. These cases correspond to such instances in the Danish practice, when the police authorities necessarily must demand a medicolegal investigation, while the technical postmortem observations do not directly interest them.

About 1,100 postmortem examinations were carried out at the institute in 1924; of these, one third were "gerichtlich-medizinisch," and the remainder "sanitäts-polizeiliche."

The reports of postmortem observations are, generally, somewhat more elaborate, and bring out many more particulars, than is considered necessary. It seems that in ordinary cases less detail might be preferable, but this, after all, is a matter of opinion.

The technic is the common method, except in the opening of the cranium; this is performed so that the division is continued down through the cerebrum, the upper part of which is removed along with the theca cranii.

The first examination of the bodies, including the legal inspection, usually is done somewhere other than in the institute—in the proper police station—by the local police or municipal physician, whereupon the body is conveyed to the institute with a request for a postmortem examination of one or the other kind.

The archives of the institute contain a voluminous, but well arranged, collection of reports, out of which anybody, even strangers, will be able to glean the most valuable details recorded in the extensive and varied cumulative experience of the institute. With the greatest liberality this material is placed at the disposal of the large number of visiting physicians.

The institute adjoins immediately the Institute of Pathological Anatomy (chief, Professor Maresch), a large, somewhat old-fashioned, substantial building, which contains two immense anatomic laboratories. Here, more than

3,000 bodies are examined every year—during the Great War, about 3,500; it is of interest that the entries in the journal of postmortem examinations have been continued without interruption since the time of Rokitsky (professor from 1834 to 1875), the record in 1925 reaching the number of 170,220. The museum of this institution is rich in good preparations, but neither its arrangement nor its educational value is equal to that of the Pathologic-Anatomical Museum at the Copenhagen University, the latter being, in this respect, unique.

The author had an opportunity to obtain an impression of the examinations ("Prüfungen") at the institute. They are organized differently from those in Denmark; half a dozen candidates are seated in a semicircle around a table, whereupon the professor (without the aid of censors) subjects them to a running examination. If one candidate misses an answer, the examiner proceeds to the next, and so on, until the answer is satisfactory. This method is advantageous in that each candidate is tried in one or more problems, but it hardly can be said to excel over the usual method of examining one person at a time. This mass examination does not profess perfection, but it is the most practical under the circumstances; it would be impossible to go into the qualifications of each candidate when so many present themselves, not only local students, but students from the entire German-speaking area, and many from foreign countries. The rating of the results is simple: excellent, satisfactory and unsatisfactory ("Ausgezeichnet," "genügend" and "nicht genügend"). The many who receive the last named mark and thus are "flunked" are consoled by the fact that they are free to present themselves as candidates for a new examination three months later.

Besides the chief, five medical men are attached to the institute: Professors Meisxner, Jellinek, Werkgartner, Schneider and Frauendorfer. The older men hold their positions for life, because a rapidly changing personnel cannot do full justice to the absorbing routine involved in the daily work. This work, in view of the size of the staff, is considerable, not only by its volume, but especially on account of the frequency with which the members, including the chief, are called into the courts. The principle of "the personal explanation and cross-examination of experts" is thoroughly adhered to by all courts. This form of expert testimony replaces the institution known in Denmark as the Medico-Legal Board ("Retslægeraadet"), with its predominant written testimonies in all cases. Both methods have their strong sides; the best probably is a mixture of both methods, suited to particular circumstances.

A special department of the museum of the institute is the so-called "electro-pathological" collection, with its adjunct, the Lightning-Museum ("Blitz-Museum"). This has its separate rooms and probably is the only one of its kind. It consists of an extraordinarily comprehensive collection, partly of objects derived from the fatal effects of electric discharges, and partly of articles and contrivances pertaining to such accidents. The preparations are derived from the greatest variety of electric applications, as well as from strokes of lightning. Professor Jellinek has charge of this section of the museum, and he devotes his efforts to elucidation of the subject and all its allied problems.

Partly owing to the kindness of Professor Haberda, and partly through letters of introduction, Fog was permitted to gain some insight into the activities of the police force. The director of police, Dr. Schultz, received him with great kindness and made it possible for him to study the facts and conditions of special importance for his purpose. Thus, he was allowed to inspect the entire museum pertaining to the director's office—corresponding to the "Criminological Museum" of Denmark; and in this way he obtained an

insight into the manifold objects, photographs and descriptions of contrivances, which open a view to the abyss of criminal activities growing out of the varied life of a city of such size. Curiously, the walls of this museum are covered with paintings and water-color sketches derived from a large number of social forms of life more or less directly influenced by police activity.

Fog also inspected the various special police departments and gained an insight into their daily routine. He visited the prison immediately connected with the police directorate. It is large, but of a somewhat older type than its sister institutions. Fog also visited the Criminological Institute of the university, in charge of Professor Glisbach, a jurist; likewise, the Criminological Laboratory of Dr. Türkel, a private institution closely allied to the activities of the police. One of the special functions of the latter institution is photomicrography of all kinds of objects by the aid of special lighting apparatus, such as an ultraviolet light reflected through quartz prisms, which gives rise to contrast effects revealing minute differences in the various parts of the object most effectively. This method is especially useful in the deciphering of difficult and unreadable writing on the background on a paper rendered fluorescent, the writing giving a different reaction to the light.

The author's chief impression of Vienna, and especially of his visit at the Medico-Legal Institute, was that it was a place where careful and painstaking work is done. This work has been systematized in a manner suited for imitation by other nations. Physicians engaged in legal work, and other officials, will be sure, not only of a profitable visit, but of a kind and considerate reception.

PARIS

Institutions of Older Date.—The Parisian morgues represent such an interesting chapter of medicolegal history of that city that the main features of their administration deserve to be recalled and related. The following brief sketch is based on the communication of Balthazard cited later.

In a city such as Paris, which, like many other large towns, is built on the banks of a river, the stream naturally becomes the drain of many objects pertaining to dark deeds. In such cities, the identification of drowned persons and other dead bodies forms a most conspicuous function in practical medicolegal work. Therefore, it is far from accidental that the historic "morgues" were located in the immediate neighborhood of the Seine. The same is true of the new Medico-Legal Institute.

As long ago as the fourteenth century, several contemporaneous "morgues" can be traced in different parts of the city. Bodies which had lain in these places one or two days without being identified were buried in the "cemetery of the unknown" by the aid of the nuns at St. Catherine's Convent, who seem to have been careful in relegating those of supposed suicides to a nonconsecrated resting-place.

Not until the end of the seventeenth century does one obtain exact information about the morgue in the basement of the Petit Châtelet, where everybody was free to make observations through an air-channel opening in the courtyard. In general, the detention room of each prison—the room where everybody detained by the authorities for any reason was placed for safe keeping—bore the designation of "morgue," derived from "morguer," to observe closely and authoritatively. Thus, certain prisons were equipped with two morgues, one for the living and another for the dead. They shared the general personnel of the prison. This arrangement explains a number of old accounts, some drastic and evidently overdrawn, of the treatment to which prisoners were

exposed in these morgues; and mistakes were made owing to a confusion of their double purpose.

In time, however, the dead and the living were duly separated. In 1804, a new morgue, exclusively for dead bodies, was established in an old building close to Quai Marché-Neuf, in the neighborhood of Pont Saint-Michel. It existed until 1864. Here, a postmortem room was fitted up; it was primitive, but sufficiently effective to mark the institution as medicolegal, both practically and theoretically.

This, then, was the public identification room for many years, and all unidentified bodies reposed there, free of access to everybody. The "salle d'exposition" remained as instituted for nearly a century, and, in spite of the dignity of death in all its forms, no change was made in its administration. At the outset, a simple iron fence separated the public from the part of the hall in which the bodies reposed, but a lithograph dated 1825 shows that this fence in time was replaced by a glass partition, to prevent the undue spread of the putrid gasses. Numerous other pictures of early days bear witness to the more or less drastic episodes and the painful scenes enacted in this place, but show also with what interest the public congregated about these uncanny sights, and the sensational developments derived from the misery of sorrowing relatives and the indifference of the guards—while the dead reposed there, witnesses of the horror of death and the law of final dissolution. In many respects, the simplest demands of hygiene and propriety were violated, and even the space was surprisingly limited. A curious fact was that the rooms above the identification halls were the residence of the registrar and the custodian; and it is known that in 1825 these families included a number of young girls, who amused themselves by arranging flower decorations in the windows of the morgue, while a piano had its place in a room directly above the one devoted to postmortem examinations. An author of that period (Jules Janin) wrote a novel depicting a festivity in the family of the custodian. The friends of the family imbibed liberally and sang one song after the other, but from time to time the guard approached the windows from without, lifting the red curtains and peeping inside "to ascertain whether anybody had sneaked in to steal his cadavers."

Even though many such statements must be credited to the general lack of systematized efforts in public affairs, it remains certain that the conditions were far from ideal. A reconstruction of the buildings in 1830-1836 resulted in some improvements. Each body was placed on a separate bier, and the clothes of the deceased person were displayed on hooks beside the dead owner, to facilitate recognition. At that time, also, the first attempts were made to introduce a cooling system. Water from a faucet at the upper end of the bier flowed down over the body, which lay wholly naked except for a leather belt covering the lower part of the pelvis. After 1840, an attempt was made to preserve the bodies by means of alum preparations; this method roused much interest, as it was used on the body of an unknown boy, who had been killed by garotting ("le jeune Anizat"). Although the procedure was far from ideal, the public exposition of this body continued over six weeks, at the end of which time the murderer was apprehended after having killed the boy's mother and sister.

At length, however, conditions became intolerable, and it was necessary to make arrangements for a new building. It was erected at the square behind the Notre Dame Cathedral, near the Quai d'Archevêche, and was ready in 1864 and continued in use until 1923. As the building was erected on marshy grounds, the ancient banks of the Seine, considerable engineering work was

necessary, so the total expense amounted to 600,000 francs, an enormous sum according to the conception of those days. The arrangement of the interior proved as awkward as the aspect of the architecture, and the authorities did not succeed in eliminating the traditional air of misery about the place. Many tourists who had paid the traditional visit to the morgue behind Nôtre Dame will remember their impressions.

This institution did not possess any laboratories. The exposition hall, the reception room and the preserving cells conveyed a dismal impression—especially the cells, which were nothing better than a vast, barnlike shed where relatives and friends were admitted for the purpose of identifying the dead. Later, on the initiative of Brouardel, an amphitheater of modest proportions was added; this place, however, housed his famous lectures. Brouardel likewise initiated the instalment of a freezing apparatus in 1878. The principle of this system resulted in a lowering of the temperature to -16°C ., a procedure not only superfluous but even bad for special studies. In the new institute the normal temperature in the cells is -4°C ., and this is used only in the conservation of bodies which have been examined post mortem. It goes without saying that the temperature must not fall below the freezing point at the time of the postmortem examination.

Finally, in 1906, the prefect of the Seine ordered the closing of the public hall of inspection. This formed the starting-point of a new era. The continuation of the old system with all its drawbacks for so long a period probably may be credited to the well known conservatism of the French. The authorities maintained that a change might increase the number of unidentified bodies. Statistics, however, proved this contention to be unfounded. In 1902-1904, 16 per cent remained unidentified, and in 1911-1913 and 1919-1921 (i. e., after the abolition of the old system), the figure rose to 21 per cent, but the system of identification naturally improved in proportion. This proportion is far from satisfactory—it indicates clearly the conditions in a world city. In Copenhagen, the percentage of unidentified bodies not only is far smaller, but applies practically only to infants.

The absolute numbers tell the same significant story. In 1840, 340 bodies were brought to the morgues. In 1921, this number had risen to 1,420—i. e., four or five times the number of sixty years before—with 800 postmortem examinations.

A systematic method of identification by photography was instituted by Bertillon, but its proper application awaited the new era, which was ushered in only recently.

Brouardel, who officiated from 1879 to 1906, made an effort toward the development of a new institute in 1882, but not until 1912 did the movement take definite form. Then Thoinot (1906-1913) gave definite advice and undertook a tour of inspection of the forensic institutions in Germany, Austria and Denmark. This was two years after the inauguration of the new system in Copenhagen, which received full justice in Thoinot's report in the *Annales d'hygiène publique et de médecine légale*, March, 1912. The World War, however, directed the flow of public money into different channels, and the erection of new buildings was interrupted. Finally, in 1920, the work was continued under the advisement of Balthazard, and in 1923 it was finished.

In 1920, Fog visited the old institute and saw how primitive the whole equipment was. It conveyed to the visitor rather the spirit of historical decay than that of a municipal institution for the adjustment of daily social irregularities. At that time, too, the prefecture of police demanded of the visitor

not only his pass, but his diploma of academic medical education—in vivid contradistinction to the open and easy practice of former days.

In 1926, the author witnessed the leveling of the old, sordid spot behind *Nôtre-Dame*. This was being converted into a park, and garden soil had been spread over the ruins of the ancient morgue. In the future, children will play and flowers bloom there: *Les extrêmes s'y touchent*.

The New Institute.—The new institute, opened on the first day of April, 1926, also is located on the banks of the *Seine*. It is a modern, two-story, solid building, surrounded by spacious grounds at the *Place Mazas*. A beautiful garden faces the front, toward the *Pont d'Austerlitz*.

This excellent institution stands out as the result of an intimate cooperation between the prefecture of police and the faculty of medicine. Their interests being related, each administers its special department.

These departments are: administration department, department of technical studies and department of instruction.

1. The administration department, allied to the prefecture of police, is open to the public. It contains the necessary offices, work rooms and space for the accommodation of official archives. This department also superintends the inspection hall where the unidentified bodies are conveyed from the ground floor after having undergone a preliminary treatment. This hall is divided into two parts by a glass partition in order to avoid the diffusion of odors. Here, clothing and other property are inspected by relatives and friends. Further, there are well appointed accommodations for the transfer of the bodies into the care of the family—a room furnished like a chapel, with a catafalque for the coffin; also, an adjoining waiting room for visitors and callers. The rooms are all duplicated and the suites mutually separated, in order to avoid any painful waiting on the part of relatives or any hurried departure of processions when in progress.

2. The technical division, entirely inaccessible to the public, includes the following accommodations:

(a) In the basement are ninety-six cells for the reception and storage of adult bodies. They are arranged in double tiers, one above the other, at both sides of a central passage. Adjoining this is a smaller tier reserved for bodies of an infectious character, or such as have been received in a more or less advanced state of decomposition. All these cells are equipped with an electric system of ventilation. Some cells also are reserved for the bodies of children and for organs which demand a toxicologic study. All bodies are placed in water-tight coffins of wood. The large number of cells will admit the proper provision for possible catastrophes.

(b) There are a boiler room and a freezing plant (ammonia system) with electric motors. The standard temperature in the cells is -4°C .

(c) Adjoining the storage vault is a spacious, airy inspection hall where the bodies are inspected, undressed and cleaned, preparatory to the legal examination. This is supplemented by an autoclave for the disinfection of clothing, etc., their registration and storing. Finally, bathing accommodations are supplied for the officials.

(d) Stables and kennels are provided for animals used in experiments and tests.

On the first floor are two postmortem laboratories, in charge of the prefecture of police. The work is done by "*les médecines légistes*." One of these laboratories, designed for bodies in a state of initial decomposition, is located in the basement. All are connected by elevators. Thus, the rooms on the first

floor are reasonably protected against the spread of gases. Immediately adjoining the laboratories are a photographic plant with a dark-room, and bath rooms as well as parlors for the officials.

3. The department of instruction is governed by the medical faculty. It has an amphitheater (capacity 200) with a large table and a lantern apparatus. There are also laboratories for special studies (blood, hair, sperma, etc.), a toxicologic laboratory, a seminar room with a capacity of forty students and, further, a library which contains the integral parts of the private collections of previous professors of legal medicine. In the hallway are portrait busts of these men: Orfila (1819-1822), Tardieu (1861-1879) and Brouardel (1879-1906). Finally, there is the museum, which is still relatively small, mainly because of the limited space available until the opening of the new institute.

The aim of the instruction is to meet the demands of the medical students generally, and to educate "médecins légistes," who also receive courses in legal psychiatry, traumatics, occupational diseases, war invalidity, etc. Finally, special courses are given by jurists and criminologists, as a part of the education offered by the "Institut de criminologie."

The three departments, thus, have separate administration connection and yet form a harmonious unit, connected by the beautiful building with its light, airy halls. The general public has no access either to the technical department or to that of instruction. Entrances and exits are located with this in view; there is a special gate for funeral processions, a special entrance for students, another for witnesses to the identifications and so forth. The rooms of the administration staff surround an inner court, the so-called "antrium," which is artistically planted with flowers. The one wall of this court is divided into three niches, decorated with frescos; the central one of these shows the picture of a young woman picking golden apples from the tree of knowledge. The inscription above this painting is: "Par la science, la nature instruit l'humanité."

The technic used in legal postmortem examinations excludes the median section. Instead, the entire front of abdomen and thorax (including the sternum and costae) is lifted off, like a large shield. Thereupon, the cavities are studied, and the organs examined, one by one, as they are lifted out. The cerebrum is divided on a horizontal plane, as in the Vienna institute.

The amount of material studied will be evident from the figures of the year 1925: bodies treated, 1881 (of these, infants and embryos, 241); about 10 per cent unidentified; postmortem examinations, 1,070; toxicologic investigations (for Paris and the Seine Department), 35.

This elaborate activity shows the advantage of having the administrative functions and the scientific work divided between the police and the Medical Faculty, respectively. The only drawback is that inasmuch as most postmortem examinations are carried out by the "médecins légistes," who function under the prefecture of police, only a small number of these studies can be done by the men who are intimately associated with medical education. This system is characteristic for France as compared with the Scandinavian and the Germanic countries.

The medical officers connected with the Medical Faculty at present are: Professor Balthazard, (chief, since 1920), Professor Duvoir, Professor Dervieux, Professor Piédelièvre and Dr. Philippe.

BIBLIOGRAPHY

Balthazard: Les morgues Parisiennes anciennes, *Ann. de méd. lég.*, January, 1923; L'institute médico-légal de l'université de Paris, *Ann. de méd. lég.*, July, 1923.

Haberda: Geschichte des Wiener Lehrkanzels für gerichtliche Medizin, Beitr. z. gerichtl. Med., 1911, vol. 1; Zur Eröffnung der neuen Räume des Instituts für gerichtliche Medizin in Wien, Dec. 12, 1922; Wien. klin. Wchnschr., 1922, p. 978.

Technical

DEATH IN CONNECTION WITH LUMBAR PUNCTURE. LESKER M. WIEDER, Am. J. M. Sc. **173**:854, 1927.

Routine lumbar puncture in the syphilitic patient is a comparatively safe procedure; death followed puncture in a ratio of less than 1 in 13,000 cases in the clinic described (University of Michigan). Of the two deaths only one could be definitely ascribed to the lumbar puncture (purulent meningitis). In addition to aseptic technic, only routine precautions, such as subsequent rest in bed with elevation of the foot of the bed, are necessary in spinal puncture in the syphilitic patient. The case described is one which presented evidence of enormous postpuncture leakage of the spinal fluid. The question of the relation of this leakage to the death of the patient is complicated by the evidence of syphilitic involvement of the central nervous system and by the thymicolymphatic constitution.

AUTHOR'S SUMMARY.

DETERMINATION OF BRONCHOSPASM IN THE GUINEA-PIG. K. K. KOESSLER and J. H. LEWIS, Arch. Int. Med. **39**:163, 1927.

Large guinea-pigs (from 500 to 800 Gm.), anesthetized with ether, are used. The trachea and external jugular vein are prepared for ligation; the skull at the occiput is perforated and the medulla and cord destroyed with a piece of stiff wire. A cannula is tied into the trachea and artificial respiration set up, compressed air from a tank being introduced intermittently by an interrupting valve controlled by a small motor. The inflation pressure is measured by a manometer and controlled by an escapement valve. The respiration rate should be about 22 a minute. The air escapes from the lungs through a small glass T tube inserted just above the tracheal cannula. The heart continues to beat for hours if these procedures are carried out successfully. Finally, a glass cannula is tied into the jugular vein and connected by rubber tubing with a buret filled with salt solution; solutions the effect of which is to be tested are injected into the lumen of the rubber tubing. The changes in intrathoracic pressure are registered on a tambour by inserting a perforated needle into the chest cavity and connecting it with rubber tubing to the tambour to form a closed system. This method has been found useful in studying anaphylaxis and anaphylactoid phenomena.

S. A. LEVINSON.

SPECTROPHOTOMETRIC ANALYSIS OF BLOOD SERUM IN NORMAL AND IN PATHOLOGIC CONDITIONS. T. B. MAGATH and C. SHEARD, Arch. Int. Med. **39**:214, 1927.

The yellow pigment in the blood serum is bilirubin in normal persons, and in those suffering from malaria, pernicious anemia, hemolytic icterus and jaundice due to obstruction of bile. The degree of bilirubinemia varies and the order named indicates the relative amounts. If the bilirubins are different, it is not shown in the type of spectrophotometric curve. Usually one hour after transfusion in cases of pernicious anemia, the serum shows an increase in bilirubin. Any process causing too rapid destruction of blood or too slow excretion of bile results in retention of bilirubin. Combinations of both factors probably play a part in the clinical picture and the spectral analysis. Fundamentally, all jaundice is hemolytic.

AUTHOR'S SUMMARY (S. A. LEVINSON).

RELATION OF HEMOGLOBIN, CELL COUNT AND VOLUME TO ERYTHROCYTE SEDIMENTATION. E. H. RUBIN and NORMAN N. SMITH, Arch. Int. Med. **39**: 303, 1927.

By the use of hirudinized blood, it was found that the lower the cell volume (hematocrit), the more rapid is the sedimentation.

SIGNIFICANCE OF H-ION CONCENTRATION FOR THE COLLOIDAL GOLD TEST. O WUTH and M. FOUPEL, Bull. Johns Hopkins Hosp. **40**:297, 1927

A new method for the preparation of colloidal gold is described based on H-ion concentration and addition of a protective colloid. The influence of the H-ion concentration has been demonstrated. In "aging" colloidal gold becomes more alkaline and less active, hence for the test the colloidal gold should be freshly prepared.

NOTE ON THE EFFECT OF POTASSIUM IODIDE IN THE SHAFFER-HARTMANN MICRO SUGAR REAGENT. W. A. DE LONG, J. Biol. Chem. **72**:731, 1927.

The incorporation of potassium iodide into the combined Shaffer-Hartmann micro sugar reagent greatly decreases its sensitivity. Accurate values may be obtained in the estimation of blood sugar with this reagent only when the iodide is added after the initial reduction of copper-sugar is complete.

ARTHUR LOCKE.

A MODIFIED ELECTRO-GUTZEIT APPARATUS FOR THE QUANTITATIVE ESTIMATION OF MINUTE AMOUNTS OF ARSENIC IN INSECT TISSUE. D. E. FINK, J. Biol. Chem. **72**:737, 1927.

The electro-Gutzeit method for the recognition and estimation of traces of substances containing arsenic depends on the productions of arsine from an acid solution of these substances through the reducing action of electrolytically evolved hydrogen. The new apparatus permits the detection of 0.00002 mg. of arsenious acid, and of 0.001 mg. of arsenic without a previous destruction of the organic matter in the test sample.

ARTHUR LOCKE.

A COMBINED DILUTING AND STAINING FLUID FOR DIFFERENTIAL LEUCOCYTE COUNTS IN THE COUNTING CHAMBER. D. NICHOLSON, J. Lab. & Clin. Med. **12**:548, 1927.

The leukocytes are not evenly distributed on a glass slide and it is impossible to do an accurate differential count of them by this method. The leukocytes are evenly distributed in the counting chamber, and if 6 per cent Giemsa's stain in 20 per cent acetone is used as a diluting fluid, the red cells are rendered transparent and the leukocytes well stained so that a differential count can be made under the high power. A fresh mixture of Giemsa's stain and acetone solution must be made daily. Even faint traces of acid or alkali interfere with the staining.

S. A. LEVINSON.

THE VALUE OF LIPIODOL IN THE DIAGNOSIS AND TREATMENT OF ABSCESS OF THE LUNG. H. C. BALLON, Surg. Gynec. Obst. **44**:1, 1927.

Ballon reviews ninety-four cases of abscess of the lung, 25 per cent of which followed operations about the mouth and throat. Errors in diagnosis based on the so-called typical history are illustrated. The relative infrequency of a

demonstrable cavity with fluid level by the ordinary roentgen ray in chronic abscess of lung is noted. Ordinary roentgen ray per se in many instances gave an ill defined anatomic localization of the site of disease, and even a false impression of the extent of disease which clinical examination often failed to correct. The use of iodized oil, 40 per cent, by the bronchoscopic method, when combined with a definite routine examination, is of undoubted value and better results will be obtained when the surrounding parenchyma and bronchial architecture are completely defined. Reactions were not noted from the use of iodized oil in this form of lung suppuration.

M. L. PARKER.

THE PRESENT STATUS OF TURBIDITY MEASUREMENTS. P. V. WELLS, *Chemical Rev.* **3**:331, 1927.

It is evident from the work cited that turbidimetry takes its place beside colorimetry as an extremely sensitive method of volumetric chemical analysis. It is already a standard method in the analysis of water and established its usefulness on toxic smokes during the war, and on the pollution of air by dust particles. Many raw commercial products are turbid, and must be filtered. Turbidity is a convenient measure of filtration efficiency. To grade the size of particles of pigment, etc., turbidity is a direct statistical measure much more readily determined than the laborious methods of the microscope and ultramicroscope. Tyndallmeters and turbidimeters are particularly adapted to the study of the kinetics of precipitation, coagulation and peptization reactions, and transformations in sols and gels. Critical opalescence is a sensitive indicator of the critical state.

In the biochemical analysis of blood, urine, spinal fluid, etc., the method has already shown its usefulness, particularly for the proteins for which comparable color reactions have not been found. The extremely sensitive and specific enzyme and precipitin reactions will doubtless yield information by its application. In the standardization of vaccines, and the counting of bacteria and blood corpuscles, some work has already been done. But its field par excellence will undoubtedly be in chemical pathology, for living structures are so delicate that brute methods must destroy the very phenomena they are intended to portray.

AUTHOR'S SUMMARY.

FRACTIONAL ANALYSIS OF THE GASTRIC CONTENTS. R. J. DUTHRIE, *Quart. J. Med.* **20**:265, 1927.

Two tubes were sutured together so that the bulbs were 8 inches (20 cm.) apart, thus giving a double stomach tube, and the contents removed from each tube came from different parts of the stomach—that from the longer tube came from the pylorus and the other from 7 to 8 inches (17.7 to 20 cm.) nearer the cardiac end. Considerable variation was found in the free hydrochloric acid and total chlorides in the two portions of the stomach. The curves were plotted as in a fractional test.

N. ENZER.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, May 9, 1927

LLOYD ARNOLD, *President, in the Chair*

THE PURIFICATION AND NATURE OF DIPHTHERIA TOXIN. ARTHUR LOCKE and EDNA R. MAIN. (From the Henry Baird Favill Laboratory of St. Luke's Hospital.)

Diphtheria toxin may be partially purified by a method of fractional iso-electric precipitation. The toxic and antigenic principles are flocculated from the crude broth filtrate by adjustment of the p_H to 3.3—3.8 with 0.035 normal solution of hydrochloric acid; the sediment is collected by centrifugalization, washed and dissolved in 0.005 normal solution of sodium hydroxide; and the alkaline solution is fractionally precipitated after the addition of salt to isotonicity. Two fractions are obtained, one of which is olive green, flocculates at p_H 5.0—5.2 and contains all the toxic and antitoxin-binding capacity of the original broth filtrate, associated with less than 0.001 mg. of nitrogen per Lf unit. It is not pure toxin. The other fraction is colorless, flocculates at p_H 4.0—4.06, is nontoxic, nonantitoxin binding, but does precipitate with antitoxin serums. It constitutes more than 50 per cent of the raw precipitate and may be classified as precipitinogen. Both fractions give a mauve biuret, positive Millon, xanthoproteic, Molisch and sugar-reduction reactions. The tests for phosphate and reduced sulphur are negative so far. The chemical and physical properties of the precipitates indicate the presence of a mucin, either as an impurity or as an integral cementing or binding constituent.

CHEMICAL ALTERATIONS IN THE LYMPH DURING BACILLARY SHOCK. WILLIAM F. PETERSEN and GEORGE MILLES.

A series of experiments were conducted to investigate further the autonomic balance.

The thoracic duct in quiet, normal animals was incannulated under local anesthetic, and samples of lymph were collected at intervals of from five to fifteen minutes. A saline suspension of *B. coli*, about 5,000,000 organisms per cubic centimeter, was injected continuously by means of a Woodyatt pump at the rate of from 0.5 to 1 cc. per minute after a control period of from one-half to one hour.

The calcium was determined by the method of Kramer and Tisdall, and the potassium by the same method somewhat modified. The proteins were determined refractometrically, and the sugars by the micro-Benedict method.

The ratio of potassium to calcium changed following injection. Most often it dropped, though in a few animals having a low ratio in the control period, the reverse occurred. These minor fluctuations were brought out particularly by determinations made at short intervals and were superimposed on gross changes in the general level which occurred over long periods. The animals had a tendency throughout to return to the original status, and, as is usually noted, to overcorrection. As death approached, this corrective or protective mechanism failed, and a sharp steady drop in the ratio occurred. In some cases this phenomenon was masked by the liberation of potassium into the lymph by hemolyzed red cells.

There is, as would be expected, a distinct relation between the various constituents of the lymph. For example, the ratio of potassium to calcium and the

lymph sugar show mirror images of each other in their curves; that is, with the upward trend of the one a corresponding drop is noted in the other, a relationship which often persists even until the death of the animal. Occasionally an animal was found in which this was reversed.

Similarly, the concentration of the lymph as indicated by the lymph proteins tended to mirror the ratio of potassium to calcium, and here, as before, an occasional animal showed a reverse reaction.

The carbon dioxide in general tended to drop as the experiment proceeded, indicating a progressive acidosis, but with each sharp rise in the ratio—i.e., an increase in the lymph potassium, usually absolute—the value of the carbon dioxide rose.

The urine regularly ceased flowing with a sharp rise in the ratio, and the flow was resumed with a fall, especially in the early periods when the animal still had sufficient resistance to recover. In one instance blood appeared in the urine with the final drop. A drop in the ratio occurred with the onset of a chill, and it rose with the end of the chill.

On the basis of these experiments and in the light of previous work, we have concluded that the presence of a low potassium-calcium ratio in the lymph (one below 1.75) is associated with a high degree of permeability in the visceral organs, as is indicated particularly by the passage into that fluid of such large molecules as those of the proteins. In other words, this is a state of visceral parasympathetic orientation or activity during which the permeability does not exceed the bounds of recovery. A high ratio is indicative of a sympathetic status, that is, decreased permeability.

With the break occurring in the recovery mechanism of the animal an irreversible change in the balance and more or less permanent injury to the organism result. At the same time a rapid increase in permeability occurs, the potassium-calcium ratio drops, and, since at this place the liver is exhausted of sugar, the lymph sugar drops. In the animals that still have available sugar, however, it rises sharply.

A CASE OF AGRANULAR BRONCHONCARDIASIS. RUTH TUNNICLIFF and HARRY L. HUBER. (From the John McCormick Institute for Infectious Diseases.)

Within the past few years there have been numerous reports of unusual infections of man with higher bacteria, and we wish to present one we have studied for more than two years.

The patient, Rose G., aged 21, a native of Sicily, was brought to America by her parents during her eighth year. She had always been well, but at the age of 14 she had had a respiratory infection which was diagnosed as pneumonia. After recovery she was well, but, as she did not gain in weight, tonsillectomy seemed to be indicated. During the operation, under ether anesthesia, at her home, she revived sufficiently to tear away all instruments and had to be held forcibly until ether was administered again. Following this, she had a high fever and a dry cough for several weeks and then slowly improved, but the cough persisted. She went to work, changing positions frequently because her cough disturbed other workers. About a year later, she began to expectorate small amounts of a thick, creamy sputum.

She was seen in the Respiratory Clinic at Rush Medical College, in February, 1924, when she was 18 years of age. A diagnosis of nontuberculous abscess of the lung and bronchiectasis was made. Repeated examinations of the thick, creamy, almost odorless sputum showed numerous masses of fine bacilli-like structures. Attempts to grow this organism on all types of mediums failed at this time, and as the patient did not improve under medical management, she was sent into the hospital to have the abscess drained. Her temperature seldom rose above 99.2 F., and the blood and urine were normal. Following this operation, her general condition improved, and she gained some weight, but six months later she returned to the hospital to have drainage reestablished. Further attempts to determine the type of organism were made at this time, with the following results.

Granules were not observed in the sputum. Smear preparations contained many slender rods with rounded ends, about 5 microns in length and one-half micron in width (figs. 1 and 2). Some filamentous forms, but no clubs or branching forms, were present. The bacilli were generally arranged in clumps and were not motile. The organism took ordinary stains, was not acid-fast and was granular, the granules retaining the Gram stain. When first examined, these masses of bacilli were observed, but at that time they were not surrounded by cells. Two years later, they were often found encircled by a single or by several layers of epithelial cells mixed with polymorphonuclear leukocytes.

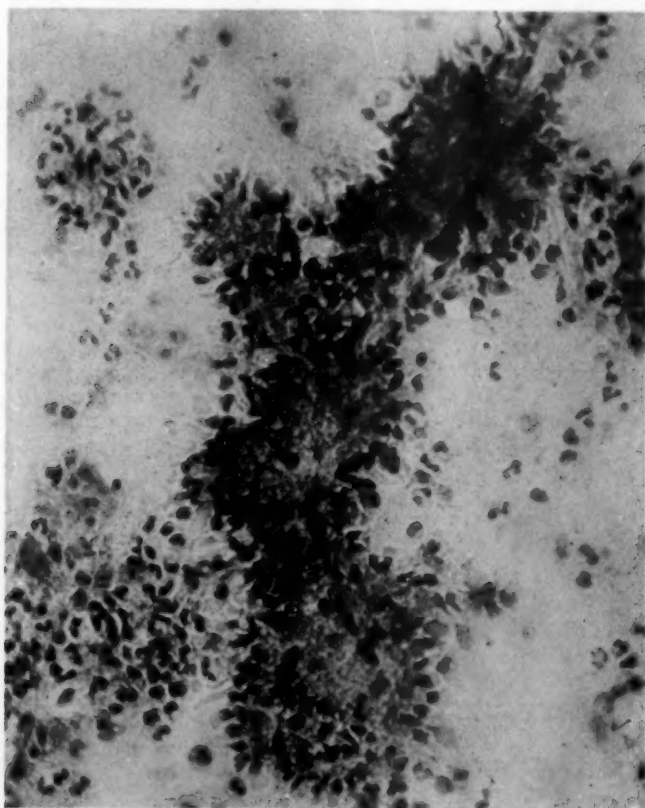


Fig. 1.—Smear preparation from sputum, showing masses of rods surrounded by cells (Giemsa stain); $\times 250$.

This arrangement may have been due to the necrosis of the bronchial cells. Usually, a variable number of eosinophil leukocytes were present.

The organism was an anaerobe, growing best at about 36 C. but also slightly at room temperature. Growth appeared generally in from twenty-four to forty-eight hours after incubation. It was difficult to grow the organism, which did not grow on blood agar or on ordinary culture mediums. The most favorable medium for its cultivation was Bacto-malt extract agar (synthetic) and malt extract agar with and without chalk. Growth rarely appeared on the surface of the agar, but when colonies did form they were of a deep cream color, soft, with regular edges and were about 1 mm. in diameter. In shake cultures growth

appeared below the surface, the colonies were lenticular and varied from the size of a pin-point to 1 mm. in diameter. The organism grew in the form of tiny balls in the fluid of condensation. A little gas was sometimes produced.

The associated streptococci died out rapidly on the maltose medium, so that the bacilli were easily isolated in pure culture.

In cultures the organism appeared as rods with rounded ends, varying from 5 to 10 microns in length and from one-half to one micron in width (figs. 3 and 4). The bacillary forms appeared singly or in palisade arrangement, the central part staining deeply, with swollen unstained ends. Some organisms had swollen ends containing deeply staining bodies. Rosette formation was rarely seen on the surface of agar, but was usual in the fluid of condensation. The rods often had swollen, unstained club-shaped ends and appeared to radiate from a central granular mass. Branching was frequent, the buds appearing to come from deeply staining bodies. Spores were not demonstrated. The organism was not

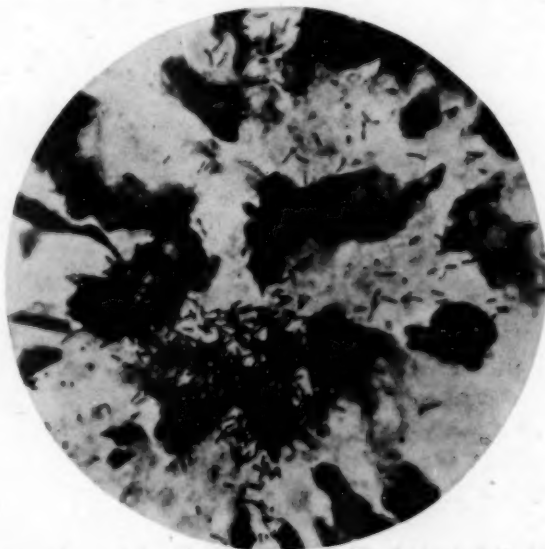


Fig. 2.—Smear preparation from sputum showing rods (carbolfuchsin stain); $\times 1,200$.

motile. The body of the rod was gram-negative, the granules retained the stain. It was not acid fast and stained with ordinary dyes.

Pure cultures of this bacillus, injected intravenously into a rabbit and intraperitoneally into guinea-pigs and mice, did not produce any lesions one month after inoculation.

This organism differs from the actinomyces usually described in not producing macroscopic granules and clubs in the tissues, and differs culturally in readily producing clubs which resemble the actinomyces clubs seen in tissues.

According to Castellani (*New Orleans M. & S. J.* 79:20, 1926), this organism seems to belong to the class of fungi of the genus *Nocardia*. The condition in the lung seems to correspond to the agranular bronchonocardiasis described by Castellani as a serious type of bronchomycosis which runs a chronic course, does not generally respond to treatment and ends fatally.

Summary—A case of agranular bronchonocardiasis is described. The sputum contained masses of slender gram-positive rods and filaments, which did not

branch or form clubs. The organism grew anaerobically on mediums containing malt, showed branching and club-shaped ends and often appeared in rosette-like masses.

SARCOMA OF THE FEMALE BREAST. A. J. PETERSEN. (From the Henry Baird Favill Laboratory of St. Luke's Hospital.)

Sarcoma of the female breast is a rare tumor. The older statistics place its frequency at about 10 per cent of all tumors of the female breast, but recent

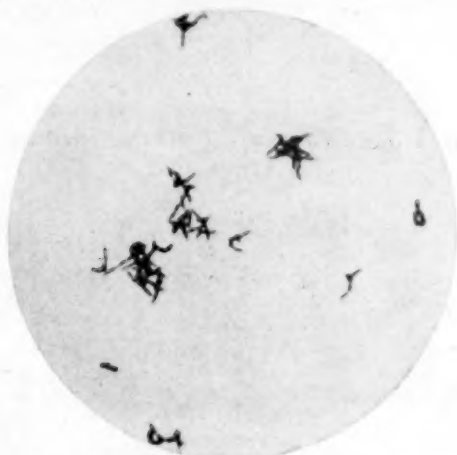


Fig. 3.—Forty-eight hour growth of pure culture in fluid of condensation of malt agar (Giemsa stain); $\times 1,000$.

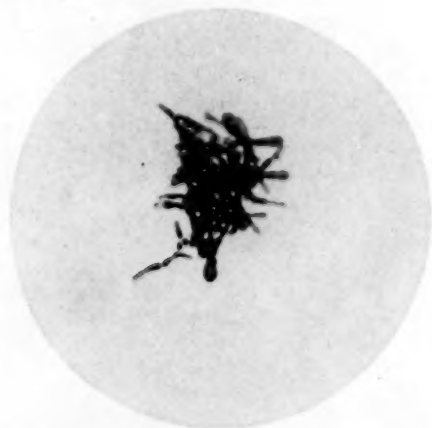


Fig. 4.—Forty-eight hour growth of pure culture in fluid of condensation of malt agar (Giemsa stain); $\times 1,200$.

figures are from 2 to 3 per cent. The reclassification and the more refined microscopic diagnostic technic in use at the present time are unquestionably responsible for this disease. Thus Poulsen (*Arch. f. klin. Chir.* **42**:593, 1891), in 1891, found that sarcoma constituted about 9.3 per cent of all mammary tumors; Williams (Connell, F. G.: *Surg. Gynec. Obst.* **4**:13, 1907), in 1894, 3.9 per cent; Gebele (*Beitr. z. klin. Chir.* **29**:167, 1901), in 1901, 9.1 per cent; Fin-

sterer (*Deutsche Ztschr. f. Chir.* **86**:352, 1906-1907), in 1907, 6 per cent; Bloodgood (Rohdenburg, G. L.: *Proc. New York Path. Soc.* **17**:112, 1917), in 1908, 2.01 per cent; Rodman (Diagnosis of Mammary Tumors, *J. A. M. A.* **56**:793, [March 18] 1911), in 1911, 2.7 per cent; Geist and Wilensky (Sutton, G. D.: *J. Michigan M. Soc.* **15**:190, 1916), in 1915, 3.9 per cent; Rohdenburg (*Proc. New York Path. Soc.* **17**:112, 1917), in 1917, 2 per cent; Deaver and McFarland (The Breast: Anomalies, Diseases, Treatment, Philadelphia, P. Blakiston's Son & Company, 1917, p. 372), in 1917, 2 per cent; Winslow (*Ann. Surg.* **74**:341, 1921), in 1921, 2.94 per cent.

The spindle cell type of breast sarcoma is the most common; it formed 68 per cent of the 156 sarcomas in Gross' (*Am. J. M. Sc.*, 1887, pp. 17, 94, 120) series, 32 per cent of the 34 in Gebele's series, and 23 per cent of the 43 in Finsterer's series. Deaver and McFarland found 206 spindle-cell sarcomas among 838 sarcomas of the breast collected from the literature up to 1917.

A summary of the reports of thirty-seven spindle-cell sarcomas of the female breast recorded in the literature from 1900 to 1925 yields the following information. (Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1919, p. 485. Graves, T. C.: *Brit. M. J.* **1**:81, 1920. Hyde, F. C.: Tumors of the Mammary Gland, *J. A. M. A.* **34**:773 [March 31] 1900. Jessup, D. S. D.: *Proc. New York Path. Soc.* **19**:117, 1919. Jopson, Speese, and White: *Ann. Surg.* **48**:662, 1908. Lee, B. J.: *Ann. Surg.* **72**:387, 1920. L'Esperance, E.: *Proc. New York Path. Soc.* **17**:112, 1917. Liell, E. N.: *South. M. J.* **1**:392, 1908. Ricketts, E.: *Am. J. Obst.* **44**:689, 1901. Rosenstein, P.: *Arch. f. klin. Chir.* **63**:555, 1901. Shere, O. M.: *Colorado M. J.* **11**:49, 1914. Speese, J.: *Ann. Surg.* **49**:428, 1909). One tumor occurred in a negro, aged 50, the others in members of the Caucasian race between the ages of 14 and 98, 66 per cent of them in women below the age of 50. The average age at which the patient first observed the tumor was 42. Fourteen of the women were married, three single, three widowed; the social condition was not given in seventeen instances. Childbirth was mentioned in the histories of less than half the married and widowed women. Etiologically, heredity played no part, while trauma was recorded in four instances. The left breast was involved in twelve cases, the right in fifteen, the position was not stated definitely in ten. The outer half of the breast was occupied by six of the eleven tumors of which the exact location in the breast was described. At first the tumor was described as a "very small lump," "pea-sized," etc. Twenty of the tumors grew slowly or remained for a period of from one to thirty-seven and one-half years, and there was rapid growth from the beginning in four. E. Ricketts reported a tumor which remained quiescent for thirty years and then grew to the size of a child's head in five months following a severe attack of influenza, which left the patient prostrated. The sarcoma attained the size of a walnut in seven instances, of a fist in ten instances, and of a child's head or larger in twenty instances. Five of the tumors were multiple; the rest were apparently single. The smaller growths were usually firm; the larger were soft and frequently contained fluid, cystic degeneration and hemorrhage. The tumor was fixed to the skin in six cases, to the pectoral muscle in three, to the thorax in two. The nipple was retracted once, and yielded a secretion or discharge in only one case. There was discoloration of the skin of the breast in seven patients, dilatation of the superficial veins of the breast in nine patients, ulceration of the breast over the tumor in nine patients. Pain appeared in the breast either early or late in sixteen instances. The axillary lymph glands were enlarged in four of the women, the supraclavicular in one. Actual infection of the lymph glands was demonstrated in only one patient prior to or at the time of the first operation. Nine tumors had capsules, but they were not always intact.

Thirty-one patients were operated on, with known recurrence of the growth in five. Three of the tumors recurred in from two to three months, two of them in from four to five years. Metastases appeared in seven patients, five of whom

had not had local recurrence following operation, and one of whom had not had an operation. The lungs were involved in three cases, the liver in four. The following organs were affected, each in one instance: brain, thyroid, ribs, mediastinum, wall of the heart, lungs, great omentum, liver, both kidneys, left ovary, pancreas, mesenteric lymph glands, vertebral bodies, muscle of the right thigh, left axillary glands, supraclavicular glands and right inguinal glands. Seven patients died following operation because of recurrence or metastasis, whereas in an equal number neither condition occurred for periods of from one and one-half to twenty-four years. The average duration of life of the former patients from the time of the initial appearance of the tumor until death was ten years; from the time of the beginning of rapid growth until death, three years. Eight patients were said to have suffered emaciation, weakness and cachexia. Seventeen other spindle cell sarcomas of the female breast (mentioned in the bibliography quoted) reported from 1900 to 1925 are not included in this summary because of insufficient data in the reports.

The first of two sarcomas of the breast reported here occurred in a well nourished, married white woman, aged 44. She was struck on the right breast in an automobile accident, and a week later noted a small lump. There was no pain at any time, but the lump gradually increased. After about two months, examination revealed two firm, freely movable nodules in the upper outer quadrant of the right breast, the largest about the size of a small orange, the other one half that size. There was no retraction of the skin of the breast or axillary adenopathy. The patient gave a history of one childbirth. A clinical diagnosis of fibro-adenoma of the right breast was made. The right breast and axillary nodes were removed in the service of Dr. L. L. McArthur, and following an uneventful recovery, the patient was given a series of roentgen-ray treatments. She is living and well four and one-half years after the appearance of the tumor.

The pathologic report (Edwin F. Hirsch) was as follows: This was a recently amputated breast with a little axillary fat, forming a tissue 30 by 16 by 6 cm. in its maximum dimensions. On the upper side was a diamond-shaped piece of skin, 19 by 7 cm. with a nipple, and in the deeper tissues were two firm masses, 6 by 5.5 cm. in their greatest dimensions. The nodule first mentioned was firm, white and translucent, with a thin capsule; the other was also firm, white in places, but mostly yellow. Lymph glands in the axillary region were as large as 2 cm. in their greatest dimensions. Microscopic examination of the tumors showed infiltrating bands and dense masses of fibrous tissues in which there were many immature spindle-shaped and irregularly shaped cells and nuclei (fig. 5). Sections of the lymph glands did not contain this tissue.

The second tumor occurred in a well-nourished, married white woman, aged 31, who had noted a small nodule about the size of an egg in the upper portion of her right breast for about eight years. This nodule began to grow more rapidly, and in a few months attained the size of an orange. The right breast was amputated in the service of Dr. W. J. Hurley, and following an uneventful recovery the patient was treated by the roentgen ray over a period of about a year. The patient was living and well two years after the beginning of rapid growth. She had never been pregnant.

The pathologic report (Edwin F. Hirsch) was as follows: This was a recently amputated female breast forming a mass of tissue when spread out about 18 by 16 by 4 cm. On the upper side was an oval piece of white skin 19 by 8 cm., with a nipple. In one place there was a tear in the tissue of the breast about 8 cm. in diameter. The lining was scarred and torn fibrous tissue. Adherent to the lining were masses of white edematous fibrous tissue from 1 to 3 cm. in diameter. On the outside of these tumor masses was the normal substance of the breast. Inside were three separate edematous pieces of white and blood-stained tissue 8 by 2 by 4.5 cm., 6 by 4 by 2 cm. and 3.5 by 2.4 by 2 cm. Sections across these pieces showed edematous white tissue mottled about 20

per cent with dark red hemorrhages. Sections of the tissue masses in the cystlike place contained edematous fibrous tissue. Portions of it were necrotic, other portions densely hyalinized. Widely scattered ducts lined with a simple columnar epithelium were found in all of these tissues. These ducts did not have the appearance of infiltrating tissue. In some of the sections the tissues were cellular, but of the connective tissue variety and seemed to be in active growth.

According to Deaver and McFarland, most mammary sarcomas are well encapsulated at first, because they usually arise through the sarcomatous transformation of benign tumors. He supports this theory by three arguments: 1. A small tumor exists in the breast for a long time, then takes on a rapidity of growth out of all proportion to the previous rate of growth and often attains

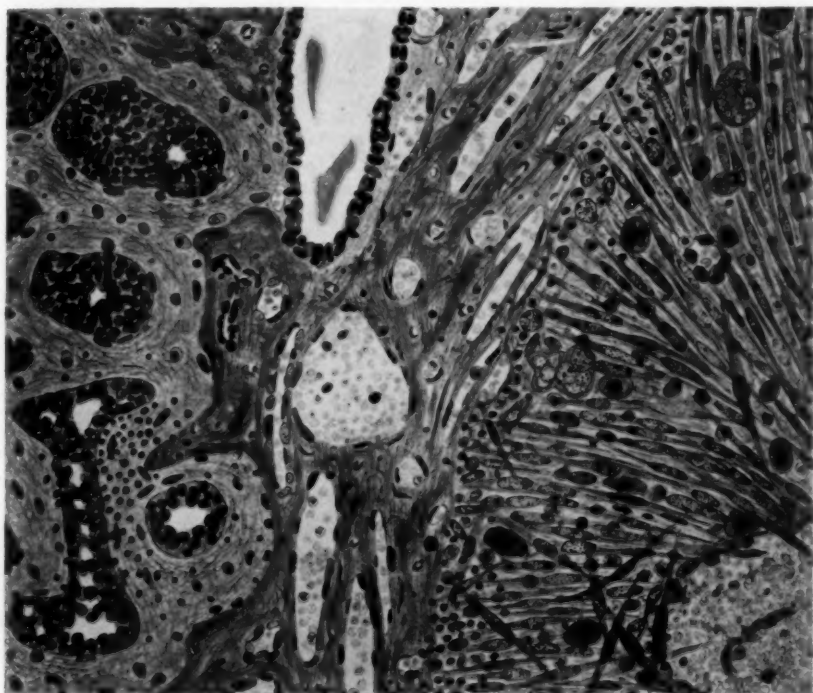


Fig. 5.—Spindle-cell sarcoma of the breast.

great size. 2. Mammary sarcomas are well encapsulated and freely movable during the early part of their existence, while sarcomas elsewhere in the body are barely surrounded by a definite membranous capsule. It is therefore concluded that mammary sarcomas derive their capsules from the benign, antecedent tumors from which they grow. 3. Mammary sarcomas are commonly described as adenosarcomas, adenocystic sarcomas or other forms, and the occurrence of epithelial glandular elements in their structure may be accounted for by supposing that they develop in tumors of glandular structure, many of whose elements persist in spite of the sarcomatous change of the connective tissue.

On the other hand, there is the relatively rare sarcoma which arises directly from the connective tissue of the breast and begins as a small tumor that grows steadily and rapidly. It rarely attains great size. Ulceration of the skin occurs early. Metastasis to the internal organs is less common than in

the first type of sarcoma described. Of the thirty-seven patients whose cases are summarized above, there were four in whom the tumor displayed immediate rapid growth, and it may be noted that metastasis occurred in but one of these.

The differential diagnosis of sarcoma of the breast is often difficult. The small recent mobile sarcoma may be taken for a fibro-adenoma, and the diagnosis depends on the histologic examination of the tumor tissue. An ulcerated sarcoma with axillary adenopathy may be mistaken for a carcinoma; but a large firm tumor of recent rapid growth, without the usual retraction of the nipple, the usual fixation of the surrounding tissues and the usual axillary involvement, should suggest sarcoma rather than carcinoma, according to Gross. The spindle cell sarcoma may be differentiated from the round cell and the giant cell sarcoma by its development at a comparatively early age, its slow recurrence after removal and the long life of the patient. The round cell sarcoma occurs at a comparatively late age, recurs rapidly, and the duration of life is relatively short. The giant cell sarcoma likewise appears late in life, but the duration of the life is remarkably long, and local recurrence is delayed longer than in the other types.

NEW YORK PATHOLOGICAL SOCIETY

Regular Monthly Meeting, May 12, 1927

DAVID MARINE, *President, in the Chair*

A CASE OF RHEUMATIC PANCARDITIS, PRESENTING UNUSUAL AORTIC AND ARTERIAL LESIONS. WILLIAM C. VON GLAHN. (From the Department of Pathology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.)

The following case of rheumatic endocarditis, involving the tricuspid, mitral and aortic valves and the left auricle, with acute rheumatic pericarditis and myocarditis, is believed to be worthy of report because of certain lesions discovered in the aorta and the larger arteries, and these lesions are considered to be of rheumatic origin. Rheumatic lesions of the aorta of a gross nature have been described as an extension of the process from the aortic valves. In the case described here, the lesions were found at so great a distance from the valves that there could be no question of extension, and the process must have been an independent one. The changes occurring in the larger arteries differ from those of the usual acute arteritis and present features that can be correlated because of their similarity with the alterations produced in the left auricle in rheumatic disease.

History.—F. L., a white boy aged 15, was first admitted to the Presbyterian Hospital in April, 1925, with acute rheumatic fever. It was found that he had mitral stenosis and insufficiency, aortic insufficiency and cardiac insufficiency.

He was admitted for the second time in October, 1926, with lobar pneumonia (type II), acute parotitis and acute cystitis. The condition of the heart was the same as on the first admission. He was treated in the outpatient department for a sharp pain in each flank, radiating to the pubes, during January and February, 1927.

The third admission was in February, 1927, because of severe precordial pain, generalized aches and pains, and malaise. Physical examination showed: an enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency, acute pericarditis with effusion; bronchopneumonia. For a time the patient responded to salicylates. Death occurred two weeks after admission.

Autopsy.—Characteristic rheumatic endocarditis (tricuspid, mitral, aortic valves, left auricle), rheumatic pericarditis and rheumatic myocarditis were

present. In the ascending portion of the aorta were several elevated plaques of pale brown; they were translucent and glistening and were sharply differentiated from the narrow, yellow opaque arteriosclerotic streaks nearby. The celiac axis and the superior mesenteric artery were surrounded by a wide zone of gray, translucent tissue. The lumen of the mesenteric artery was narrow and crescentic in outline.

Histologic Examination.—Aorta: In section, through one of the plaques were bands of nonnucleated fibrillar material in the intima, bordered by large basophilic cells having large vesicular nuclei with a central dense clump of chromatin. Some of these cells contained two such nuclei. In arrangement and staining reaction, these cells were identical with those so characteristically present in rheumatic disease of the left auricle.

In other sections, the plaque was composed of loose tissue, made up of irregular cells tending to have a vertical arrangement and separated by indefinite fibrillar stroma. The endothelial cells covering this new tissue were polyhedral in form and appeared to migrate into the subjacent stroma. There were occasional clefts filled with red blood cells in the new tissue. No swollen fat laden cells were present as in ordinary atheroma. The internal elastic lamella, beneath the plaque, was split into two layers. The inner layer, lying immediately under the stratum of new tissue, was intact; the outer layer was interrupted by patches of avascular scar tissue, with irregular, vertically disposed cells.

The adventitia was greatly thickened and the nutrient arteries were thick walled. The medial lesions consisted of dense scar tissue or collections of cells about the penetrating vessels. Characteristic Aschoff cells were found among these accumulated cells.

Celiac Axis and Superior Mesenteric Artery: All the coats were affected. The endothelium was preserved. The intima was thickened by loose fibro-cellular tissue. The internal elastica was irregular and often was split into numerous lamellae. Many delicate elastic fibrils ran in all directions. In several areas, just internal to the internal elastica, were collections of cells composed largely of distorted polymorphonuclear leukocytes.

In the media were many polymorphonuclears, either scattered individually between the muscle fibers or collected into more compact masses.

The adventitia was thickened by dense collagenous tissue, which radiated into the surrounding fat. Many capillaries were present; the endothelium was so swollen as almost to occlude the lumen. Numerous small lymphoid cells, polymorphonuclears and large mononuclears, with basophilic cytoplasm, were also present.

Little fat was to be found in the intima and then only as fine granules in a few cells. As in the aortic lesion, this fat was not anisotropic.

Gram stains of the involved vessels did not reveal any organisms. Blood cultures, taken during the life of the patient and incubated for three weeks, did not show any growth of organisms.

The lesions in the aorta and arteries were believed to be of rheumatic origin because the character of the cell infiltration and the disposition of the new tissue were identical with those found in the left auricle in rheumatic disease, and there was no demonstrable bacterial infection.

NOTE: This case in greater detail and with illustrations will be reported elsewhere by Doctors Pappenheimer and von Glahn.

DISCUSSION

PAUL KLEMPERER: I fully agree with Dr. von Glahn in the conception of the aortic lesion as rheumatic. I have seen a case like that only lately, in which the macroscopic appearance was not so evident. The condition could not be recognized in the gross, but sections revealed an appearance identical with that described by Dr. von Glahn. The valvular lesions were insignificant;

there were only a few appearing on the mitral valve and none on the aortic valve, so I was sure it was not by way of propagation that the aorta became involved. I should like, however, to express some doubt as to whether one can conceive, with absolute certainty, of the lesions in the peripheral blood vessels as of rheumatic origin or not.

MAX GOLDZIEHER: I should like to ask Dr. von Glahn if he considers the morphologic evidence given by this observation sufficient to claim that these lesions are specifically rheumatic, or if they might be of some other inflammatory origin, similar to those nonspecific inflammatory changes described years ago, which are common in the peripheral vessels in infection in childhood, in a variety of forms, including the more common type of vascular disease as well as periarteritis nodosa?

WILLIAM VON GLAHN: I think that one has to admit there are certain resemblances between periarteritis nodosa and the rheumatic lesions in peripheral vessels. Polymorphonuclear leukocytes and often eosinophils are found in each case. The rheumatic lesion, however, so far as I know, never leads to the formation of aneurysms, and it does not assume a nodular form. In many of the involved peripheral vessels in rheumatism, there may be a coagulum of fibrin beneath the endothelium, at times with hemorrhage, but these vessels do not undergo thrombosis, which is so often seen in periarteritis nodosa. By downgrowth of the endothelium and invasion of connective tissue, the involved vessel becomes filled with a spongy mass of new capillaries. I have never seen this in periarteritis nodosa. In the peripheral vessel in the case under discussion, the intimal involvement occurred in areas over normal media, and I have not seen this in periarteritis nodosa. I have never encountered a lesion produced by periarteritis nodosa such as exists in this superior mesenteric artery and celiac axis, and the thing that makes me feel confident that this is a rheumatic lesion is the finding of exactly the same types of cells here as occur in the auricle in the rheumatic lesion. I have never found periarteritis nodosa producing a lesion such as is presented in this aorta. In this case, a great many lantern slide preparations from the auricle and aorta were compared, and they were alike. Furthermore, I do not recall having seen in periarteritis nodosa the bizarre elongate nuclei which are present in the auricle and about the peripheral vessels in rheumatic disease.

UNUSUAL TUMOR OF THE KIDNEY SIMULATING PYONEPHROSIS. ALFRED PLAUT.

After nephrotomy for removal of a kidney stone, the patient, a white woman, aged 58, developed a fistula and a swelling in the region of the kidney. A year after operation the pyelogram showed diffuse outline and widening. The pre-operative and postoperative diagnosis was pyonephrosis. The specimen was a soft, foul smelling, apparently cystic mass, 21 by 13 by 11.5 cm. Out of a small rupture in the surface some light brown thin fluid escaped. After fixation and removal of the fat, the specimen measured 10.5 by 5.5 by 5 cm. It then showed all the landmarks of a kidney. A short piece of ureter was attached; when it was opened, its mucosa seemed to have many small protrusions and the wall was 8 mm. thick. The pelvis of the kidney and the calices formed a system of irregular cavities which reached the surface of the specimen, leaving only a thin shell of tissue. The small amount of cut surface which was shown by this tissue revealed nothing of the kidney cortex or the pyramids. A group of small round cavities filled with a glairy gray substance was situated near the periphery. They formed a mass the size of a small walnut.

The microscopic picture was surprising. All the surfaces, including the ureter, were lined with what looked a great deal like mucosa of the intestine. High cylindric cells with basal nuclei forming gland-like depressions and papillary protrusions were embedded in a loose tissue which at some points even seemed to contain lymph follicles. Smooth muscle was found under it, but it did not show a regular arrangement and did not contain any nerve plexus. Circumscribed thick masses of muscle surrounded the blood vessels with thick-

ened and partly hyalinized walls. At several points under the mucosa-like structure a partially differentiated cellular tissue was seen. It consisted of medium sized, fairly regular round cells with dark nuclei. It contained agglomerations of cells which obviously were of the same character; their nuclei were a little larger and clearer, and some of the cells formed a narrow circle; in another group a small lumen was visible; the cells assumed epithelial features in shape and arrangement. The larger ducts were distinctly kidney tubules, and the whole tissue reminded one of embryonal kidney tissue or of certain areas in the so-called adenosarcomas of the kidney. In the hematoxylin eosin stain, the mucus became a dark purplish blue, while the contents of the tubules was bright red. Although both types of glandular formations were found near each other, no communication had been found so far. (Serial sections had not been made.) Corresponding to the glairy masses described in the foregoing, an adenomatous structure was found consisting of the mucous glands arranged in complicated coils, with little stroma between them. Enormous masses of mucus had been produced; it had been pressed mechanically into spaces of connective tissue and had caused there, as well as in free masses of mucus, irregular cytologic pictures by destruction of epithelial cells and destruction and regeneration of connective tissue and muscle. Leukocytic and other inflammatory infiltration was found at many spots.

The hypothesis is that this was a mixed tumor of embryonic character. The epithelial element had outgrown the other tissues. In order to explain the intestine-like structures, the starting point of the developmental anomaly which led to this tumor must be placed in an early period; the hypothesis of displaced blastomeres must be used, for, however incredible this seems, still it is more acceptable than that of metaplasia in mature tissue.

A rapid survey of the literature has not shown an analogous case.

DISCUSSION

DAVID SEECOF: Was it a right-sided nephrectomy? How far down did the ureter extend?

ALFRED PLAUT: I cannot tell you.

PAUL KLEMPERER: Have you considered the following possibility? In the extrophic bladder, tumors exactly copy the adenomas of the intestine, so much so that when I saw one of these cases I thought there must be a mix-up; however, the few cases recorded in the literature are all identical, and most of the tumors of the extrophic bladder are adenocarcinomas with sometimes an enormous formation of mucus. Some adenomas, also with the formation of mucus, have been found in the pelvis of the kidney. Such a case is recorded by Paschkis, a student of Zuckerkrandl, who was one of the first to observe the adenocarcinoma of the bladder. I should like to mention the possibility here that that condition is being dealt with. I have had the occasion to see one case of carcinoma of the extrophic bladder which was exactly like an adenocarcinoma of the intestine, and Dr. Ewing expressed the same opinion. Then I have seen one mucous carcinoma of the bladder in a normally formed bladder, so I think that one has to consider such a possibility in the case described here.

ALFRED PLAUT: I do not see any contradiction in Dr. Klemperer's conception and mine. All these cases can be explained only when one assumes that the cells have more potential factors in themselves than the usual cells of the bladder or the kidney. When one gets to the bottom of the affair, it comes down to the same explanation; only the names are different. I do not see why I should name a tumor like that a carcinoma. There is an enormous heaping-up of glandular ducts, but there are no signs of invasion. I should prefer to call it an adenoma in the kidney of embryonic origin. Does it not look like embryonic kidney tissue?

MAX GOLDZIEHER: This case is interesting to me because I had a case which reminds me somewhat of it. A cyst was found underneath the left kidney, about the size of two fists and filled with a clear, slightly mucous fluid. I thought it was a simple cyst of no particular interest, although I could not explain its origin; the cyst was lined with high cylindric epithelium exactly of the type of the intestines. The structure of the wall showed only a few small foci of lymphatic tissue. I am not positive about the diagnosis in Plaut's case, and I am not convinced that those foci are really embryonic kidney tissue. I would feel rather that this epithelium is of intestinal origin.

ALFRED PLAUT: I cannot see how an enterocytoma could assume a structure like this. There is no doubt that the specimen described is a kidney; it shows not only the form of kidney, the dilated calices and a ureter, but also a ureteral catheter has been inserted, a pyelogram taken, and a urinary fistula existed before operation. Dr. Klemperer's explanation of the tumor as an adenoma from the epithelium of the pelvis of the kidney does not explain the presence of the smooth muscle. The formation out of solid heaps of cells can be seen distinctly in some areas. I think it is impossible to explain this mechanically.

A CASE OF STREPTOTHRIX PYEMIA. PAUL W. ASCHNER. (From the Pathological Department of the Mt. Sinai Hospital.)

An iron worker, aged 49, was admitted to the hospital after six weeks' illness. The symptoms were cough, pain in the left side of the chest, fever and loss of weight and strength. The sputum, at first mucoid, became blackish, blood streaked and foul. Physical signs and roentgen-ray examination showed an infiltrating lesion of the upper lobe of the left lung, inflammatory or neoplastic in nature. The sputum was negative for tubercle bacilli. After four weeks' observation, the left upper lobe was explored under local anesthesia and was found densely infiltrated, as if by neoplasm. A specimen removed however, showed acute inflammation and organization of lung tissue. Following the intervention, there was an exacerbation of the process with involvement of the middle lobe of the right lung, and the appearance of numerous tumor-like nodules on the scalp, face, upper limbs and trunk.

One of these nodules was removed for examination and proved to be a subcutaneous abscess with a wall composed of granulation tissue, evidently a metastatic lesion. Bacterial stains were made by the Goodpasture method and revealed numerous fine gram-positive filaments showing true branching. The diagnosis of streptothrix infection of the lung with pyemia was thus made. Four blood cultures were made. Two were negative; one showed a gram-positive diphtheroid in the anaerobic tube seventeen days after the culture was made, and another showed a gram-positive higher bacterium on the aerobic media four days after the culture was made. Serologic studies were necessary to confirm this observation as the colonies did not exactly correspond with those subsequently obtained from a skin nodule. The streptothrix organisms present many variants and are closely allied to the cornybacteria (diphtheria group). Positive streptothrix blood cultures have been reported in three cases of rat bite fever, in which they are probably secondary invaders.

The patient died about three and a half months after the onset of his illness. A limited postmortem examination was made by Dr. Klemperer. Numerous subcutaneous nodules, some necrotic, were scattered over the forehead, face, trunk and upper extremities. The upper lobe of the left lung presented a grayish necrotic area 5 cm. in diameter surrounded by conglomerate nodules for another 4 cm. The rest of the lung presented scattered grayish nodules about 1 cm. in diameter. The middle lobe of the right lung was occupied by a solid mass of smaller and larger nodules with areas of central necrosis and suppuration, with a localized fibrinous visceral pleuritis. The pericardium showed several flat nodules on its external aspect. There was one small abscess of the spleen and two of the liver. Each kidney presented twenty or thirty

nodules in the cortex; they were from 1 to 3 mm. in diameter, yellowish white and grossly resembling leukemic infiltrations.

The microscopic sections of the lesions of the lungs showed in their periphery alveoli containing the micro-organisms in an early pneumonic exudate consisting of fibrin, desquamated alveolar cells and mononuclear cells. The more central parts of the lesion presented a more active polymorphonuclear leukocytic exudation with areas of necrosis. There was no resemblance to tuberculous lesions such as some authors have described. In the kidney the lesions described in the gross appear to be small infarct-like areas with infiltration by mononuclear cells, suppuration not having supervened in these lesions of more recent origin.

DISCUSSION

DAVID SEECOF: Recently, a case of streptothrix infection was seen at the Montefiore Hospital. The patient was admitted to the tuberculosis service, but the diagnosis was made on finding the characteristic gross lesions of the skin. These consisted of recurring nodules which soon broke down into small abscess formations, which, after being emptied, left deep scars. The streptothrix was cultured from the milky fluid of these abscesses.

At autopsy, the visceral lesions were practically identical with those described in Dr. Aschner's case. The circumscribed, globular, firm, grayish white nodules resembled leukemic infiltrations. A few of these nodules were found in the bone marrow of the extremities. In the sections, however, the filaments could not be found. There are references in the literature mentioning the fact that in the tissues the bacterial or spore forms rather than the filaments are seen. The lesions in the case described resembled histologically miliary abscesses, with polymorphonuclear infiltrations and central necrosis, rather than tuberculous foci.

CALCIUM DEPOSITION IN THE MEDIA OF THE AORTA. BERYL H. PAIGE and ETHEL A. MOTT. (From the Department of Pathology, Presbyterian Hospital, and the College of Physicians and Surgeons, Columbia University, New York City.)

Calcium deposition in the media of the aorta, similar to that described in 1906 by Klotz, was found in aortas in 101 cases out of a total of 627 autopsies. This type of calcification was found in vessels in which no medial changes could be seen in the gross. Microscopically, it was first found in sections cut from blocks fixed in Zenker's solution to which no acetic acid had been added, and paraffin sections from these were stained with Bullard's hematoxylin and eosin. Later, von Kossa's silver nitrate method was found to be useful in demonstrating the deposit in the media, and after its adoption in the routine examination of aortas, several instances of medial calcification were seen, which would have been missed otherwise. It was discovered that calcium was removed from aortas which, during fixation or staining, were exposed to too strong acid.

This type of medial calcification consisted of a deposition of calcium granules in the middle third of the media. These granules differed in size, and the amount of calcium deposited varied from a few granules to an amount sufficient to show in von Kossa preparations as a wide black zone. These granules lay between the elastic fibers. Often they were surrounded by a pale blue material, suggesting in its staining character a mucoid substance. Sometimes the calcium granules appeared to be packed about muscle cells in which both nuclei and cytoplasm were intact. The elastic fibers themselves showed practically no changes and could be followed in most instances through the regions in which calcium was most abundant. With Weigert's elastic tissue and van Gieson's connective tissue stains, no rupture of the elastic fibers or increase in the connective tissue was found in the zone of calcium deposition. The calcium deposits occurred at different levels throughout the aorta, and its distribution in individual vessels appeared to be patchy.

A review of some of the literature dealing with lesions of the aorta showed that there is considerable controversy among various workers as to which element in the wall of the aorta is first involved in medial calcification, but it seems probable that the granules are laid down in the "Zwischensubstanz" of the German and Russian investigators.

A summary of the statistics compiled from the series collected indicated that the process of medial calcification of the aorta occurs more often as age advances. No case was found in patients below the age of 30. The autopsies reviewed in collecting the series were grouped according to decades, and the following chart gives the percentage of cases per decade in which a medial deposition of calcium was found:

Age	Per Cent With Medial Calcification
From 30 to 39.....	3
From 40 to 49.....	17
From 50 to 59.....	29
From 60 to 69.....	41
From 70 to 79.....	69
From 80 to 89.....	50

A rough comparison of aortas of different ages indicated that the amount of calcium deposited increases with age.

The incidence of this type of medial calcification in the two sexes was determined, the incidence being 22 per cent of the men, and 17 per cent of the women.

Attempts were made to determine the possible relationship between this type of medial calcification and true atherosclerosis. Of the 101 cases showing deposition of calcium in the media, 72 showed atherosclerotic changes sufficiently marked to be included in the final anatomic diagnoses. In fourteen of these, atherosclerosis was so extensive as to be the underlying cause of the main pathologic changes. In seventeen of the remaining fifty-eight cases, there was calcification of the intima. In twelve cases the atherosclerotic process was mild. For the sake of comparison, 158 autopsies were reviewed in which medial calcification had not been seen and in which the patients were over 30. Of these, atherosclerosis was found in seventy-one, with calcification of the intima in twenty-one. While the figures are by no means conclusive, the impression is gained that the deposition of calcium in the media of the aorta is not an arteriosclerotic lesion. The relationship of this medial deposition to the Mönckeberg type of sclerosis has not yet been determined.

Numerous other pathologic lesions were found in association with this type of calcification. There were thirty-two instances of neoplasm, twenty of which were carcinomas arising in abdominal organs, and eight were sarcomas of various regions. Seventeen cases showing other cardiovascular changes, most of them rheumatic in origin, were found in the series. An interesting observation in connection with the lesions of this system was the fact that there were only two cases of rheumatic aortitis and one case of syphilitic aortitis. Among other lesions were six cases of gastric or duodenal ulcer, five cases of acute or chronic cholecystitis, three of suppurative pleurisy, three of lobar pneumonia, eight of tuberculosis, four showing deposits of calcium in the kidneys, and one case each of abscess of the brain, epidemic encephalitis, atrophy of the thyroid, atrophy of the suprarenals, hypertrophy of the prostate, Hodgkin's disease, chronic lymphatic leukemia, amyloidosis—involving the kidneys, spleen and adrenals—typhoid fever, pernicious anemia, purpura hemorrhagica, influenza, and erysipelas with a terminal streptococcus septicemia.

Since this type of deposition of calcium in the aortic media occurred in cases showing such a wide variety of pathologic conditions, it cannot be considered to be associated with any one disease process, but is, perhaps, as Klotz suggested, to be regarded as a type of senile degeneration of the arterial system.

DISCUSSION

MAX GOLDZIEHER: If I understood Dr. Paige, her opinion is that there is an essential difference in the deposition of calcium in true atherosclerosis and that separate disease which is called medial calcification. I certainly agree with this opinion, and I think one of the main features which may help maintain it is that in cases of true atherosclerosis the calcium deposits always lie in or around areas of necrosis, while in medial calcification one finds calcium in between live and undestroyed tissue, particularly in the early cases. In atherosclerosis, the calcification is most probably secondary to other lesions of the intima causing necrosis, and in medial calcification one is dealing with a metabolic disease. Several years ago, I studied the aorta in frozen section and found that the deposition of calcium was common. It seems to me that the histologic treatment of aortas is responsible for what is often found, that the presence of calcium is not observed, because slight amounts of acid may remove small traces of calcium. I should like to emphasize the acidity of the formaldehyde which may be responsible for the calcium in some of the aortas in which calcium was looked for and none was found. Either frozen sections should be used for the study of calcium, or thoroughly neutralized fixing and staining solutions.

DAVID SEECOF: Another instance showing the difference between intimal and medial sclerosis is seen in the medium sized vessels. I refer to the calcification of the media in the vessels in such organs as the thyroid and uterus in young people, when the vessels elsewhere in the body are normal. In these locations one sees the medial calcification, commonly regarded as a type of Mönckeberg arteriosclerosis, in the absence of marked intimal changes.

A CASE OF TRUE LATERAL HERMAPHRODITISM IN THE GUINEA-PIG. HENRY L. JAFFE and G. N. PAPANICOLAOU (by invitation).

The guinea-pig was 82 days of age and weighed 391 Gm. when killed. It was well nourished and its extremities were of equal size. The gross autopsy was normal except for the reproductive system. In regard to this system, the animal had a penis-like organ 17 mm. in length and 4 mm. in diameter, smaller than the normal penis of an animal of this size, approaching more the condition of a large clitoris. The urethra extended through this organ. A small external vaginal orifice was present posterior to the clitoris, which ended blindly a few millimeters from the exterior. The internal sex organs consisted of a testis, epididymis, vas deferens and seminal vesicle on the right side; and an ovary, tube and uterus on the left side. A median vagina and two small masses of prostatic tissue, one on each side of the urethra, completed the system.

In reviewing the literature, we have found only two other definite cases of lateral hermaphroditism, and this is the first case known to us in the guinea-pig.

DISCUSSION

G. N. PAPANICOLAOU (by invitation): One interesting feature of the case was hyperplasia of the uterus. As shown by the projection, the uterus was from eight to ten times larger than the normal structure. This can be explained only by the absence of the corpus luteum and the excessive secretion of follicular hormone. There were three large, active follicles. The uterine mucosa was hyperplastic. I have seen a few cases of marked endometrial hyperplasia and in all of these large secretory follicles were present, but corpora lutea were absent. This feature is interesting from the standpoint of physiologic activity of the ovarian hormones and shows the effect that the different hormones have on the uterus.

Book Reviews

THE LIFE AND WORK OF SIR PATRICK MANSON. By PHILIP H. MANSON-BAHR, D.S.O., M.D., F.R.C.P., and A. ALCOCK, C.I.E., LL.D. ABERD., F.R.S., LIEUT.-COLONEL I.M.S. (retired) Sometime Professor of Medical Zoology in the University of London at the London School of Tropical Medicine. Price, \$5.50. Pp. 273, with 12 halftone plates. New York: William Wood & Company, 1927.

After a sketch of Manson's early life in Scotland, where he was born in 1844, the author follows him to Formosa and then to Amoy, China, where he spent thirteen years as medical officer of the port and in unofficial practice. By kindness and skill he gained the confidence of his native patients in an unusual degree. He carried on an extensive practice, including surgical operations especially for elephantiasis, abscess of the liver and stone. It was here, by his own effort and single handed, with inadequate equipment and in spite of isolation and the distractions of a large practice, that he made one of the most prolific discoveries in tropical medicine, namely, the demonstration of the rôle of the mosquito in spreading human filariasis. Manson made the crucial experiment on one of his Chinese servants who harbored filarial larvae in his blood, and who for one dollar submitted to be bitten freely by mosquitoes. This was the first time that a parasite of man was shown to pass a stage of its life in the mosquito. In connection with this discovery, a statement in the brief autobiography that Manson dictated to L. W. Sambon seems of such interest that it is repeated here:

"It was evident that, fettered in sacs (their outstretched, unbroken egg-membranes) and penned within the circulatory maze, they [the filarial embryos] could not, of their own accord, leave the human body. . . . I set myself to speculate as to what the agency might be which removed and fostered the newborn *Filariae*. It must be, thought I, something that draws out the blood and therewith the organisms in the blood; moreover, seeing that *Filaria* is confined to tropical and subtropical countries, the something must have a corresponding distribution. What might it be? A tropical blood-sucker? What tropical blood-sucker? *Filaria* is a common parasite within the tropical belt, and therefore this blood-sucker must be common there also. For reasons of distribution, season and habits, neither leech, nor flea, nor bug seemed to answer the requirements. Could it be a mosquito widespread and common in the tropics? Thus I reasoned." (Short Autobiography by Sir Patrick Manson with Introduction by L. W. Sambon, *J. Trop. Med.* 25:156, 1922.)

During his stay in Amoy, Manson also made other observations of great interest. There is good reason to believe that he saw the leprosy bacillus before Hansen's discovery was published. Manson's share in the early observations on the lung fluke makes an interesting story. In order to test the idea that filarial larvae retreated to the pulmonary circulation during the day, he was on the watch for cases of hemoptysis, and one day a petty mandarin from Formosa began to spit on the floor of the consulting room. Manson was about to protest when, as he says, "disgust and anger evaporated on seeing that the sputum was tinged with blood. I transferred it to the microscope and to my

astonishment I found, not the expected filaria embryo but the operculated egg of a different and, to me, a new parasite." Without going into further detail, Manson appears to have been the first to find, in direct association with lesions in the human lung, the fluke now known as *Paragonimus westermanii*. This and certain other observations in parasitology Manson likened to finding "a sovereign when you are looking for a shilling."

Manson next settled in private practice in Hongkong (1883). Here his most important public service was his efforts on the behalf of improvement in medical education. He was the moving spirit in starting the Hongkong College of Medicine. Returning to Europe in 1899, he soon established himself as a consultant in London, and the last half of the book describes his life and activities there. His mosquito-malaria theory and his fine and inspiring relationship as friend, steady counselor and protector of Ronald Ross in his epochal work on malaria in India are described clearly and interestingly. Manson unselfishly expressed himself as claiming credit "not so much for having formulated the mosquito-malaria theory as for having discovered Ronald Ross." He was medical adviser to the Colonial Office from 1897 to 1912 and founder of the London School of Tropical Medicine. He died in 1922. In the appendix is a list of the degrees and honors conferred on him and of his publications.

This book is a significant addition to medical biography. It is a worthy record of the life and work of an outstanding and attractive figure in recent medical history. The book cannot fail to be a source of true pleasure and inspiration to the interested reader. Perhaps part of the secret of Manson's great achievements may be contained in his advice: "Never refuse to see what you do not want to see, or what might go against the views of authorities. These are just the clues to follow up, as is also, and emphatically so, the thing you have never seen or heard of before. The thing you cannot get a pigeon-hole for is the finger-point showing the way to discovery."

DIE PATHOGENEN MIKROORGANISMEN DES AUGES. By PROF. F. v. HERRENSCHWAND, Innsbruck. Price, 24 marks. Pp. 310, with 17 figures in the text and 12 colored plates. Berlin: Urban & Schwarzenberg, 1927.

The aim of this volume is not to add any more books to the already long list of clinical bacteriology in ophthalmology, but to present a study of the morphologic and biologic characteristics of all the pathogenic bacteria infecting the eyes. In carrying out this purpose, the author divides his material into three sections.

The first, or general part consists of a brief and elementary discussion of the morphology and cultural characteristics of pathogenic micro-organisms in general. It is apparently included for the enlightenment of those readers who have no previous bacteriologic knowledge, and is distinctly inferior in quality to the bulk of the volume.

To the second, or special part, is given 247 of the 310 pages. In this the author gives an excellent and detailed morphologic and biologic description of over eighty organisms which have been found to have affected the eyes. Each organism is fully described, first in its structure, and then in its cultural characteristics. Its occurrence and frequency are briefly discussed. He then gives a complete account of animal experiments which have been performed in studying the properties of the micro-organisms. The occurrence in the eye and experiments on the eye, with particular organisms, are fully discussed.

This mass of material is presented by citing the work of investigators in all of these fields; hence the book contains an extremely large and fine bibliography, which is of great value both to the bacteriologist and to the ophthalmologist. Living up to the avowed aims of the book, the clinical and pathologic descriptions of the lesions are somewhat sketchy. On mooted questions the author attempts to adopt a judicial attitude, presenting fully both sides of the case so that the reader may draw his own conclusions. Occasionally, however, he neglects to do this; as, for instance, in his chapter on sympathetic ophthalmia. The author believes that this condition is due to a micro-organism, and bases his belief on numerous cited experiments in which uveitis was caused by injecting material from diseased eyes, in some cases producing a picture similar to that of sympathetic ophthalmia. He apparently does not consider that the mere trauma of injecting this foreign material is capable in itself of producing such lesions. He states, however, that in spite of the fact that many etiologic organisms have been described for this condition, the real organism is as yet unknown, and is probably a virus which cannot be obtained by our present bacteriologic methods. The excellent experimental work of Elschmig and of Woods tending to show that the disease is anaphylactic in nature, is not even mentioned.

A complete résumé of the entire question of trachoma is given, with a detailed discussion of the rôle of the von Prowazek and inclusion bodies. The author apparently leans to the view that these are not the true cause of the disease, and indicates that in a modern conception trachoma is not really a specific disease, but a syndrome due to any physical, chemical or bacterial irritation of the conjunctivae of people with lowered resistance. He gives an interesting account of the Italian ideas of "constitutional factors predisposing to trachoma."

The third part of the book, consisting of thirty-five pages, deals with technic. This treats briefly with the obtaining of material from the different structures of the eye, staining methods, preparation of mediums, methods of cultivating organisms and animal inoculation.

On the whole, the author has fulfilled his purpose to a high degree. The book will be a useful reference volume expressing the views and results of various investigators in both bacteriology and ophthalmology, and supplemented by an excellently arranged and complete bibliography.

SHOULD WE BE VACCINATED? By BERNHARD J. STERN, Instructor of Sociology, Columbia University. Price, \$1.50. Pp. 146. New York; Harper & Brothers, 1927.

All public health workers know that their efforts to improve any given condition will be successful only after the indifference and inertia of the public are overcome. When the program of action involves artificial immunization against a communicable disease, indifference and inertia at once are reinforced by active opposition. Especially is this true of smallpox vaccination, which has been bitterly opposed from the time of Jenner's first experimental work until the present.

"Should We Be Vaccinated?" is not, as the title seems to indicate, an argument for or against vaccination, but a "critical historical study of the controversy" which analyzes "the psychologic and sociologic factors involved in the opposition." In other words, it is a successful attempt to answer the

question, "Why have we all not been vaccinated?" rather than an answer to the one which serves as a title.

The author concludes that very little change has occurred in the character of the opposition since Jenner's day. With the increase of knowledge, certain absurd assertions of that time are no longer capable of impressing the public, and they have been replaced by misleading statements and half-truths. No matter in what form the opposition is presented, it has always been a smoke screen to conceal the activities of various groups of exploiters of the public who live in fear of any form of state regulation of their activities.

The author shows the origin of every phase of the opposition, but it is to be regretted that more space has not been given to an analysis of some of the more plausible statements made by the opponents of vaccination today. For example, a person unimpressed by a statement that vaccinia is cow syphilis, might be afflicted with a reasonable doubt when confronted with the "evidence" of the failure of vaccination in the Philippines and in Germany, or with the statement of Sydenham as to the mildness of the disease in London in pre-inoculation days.

In comparing New York with Minnesota (p. 114), with respect to the sentiment against vaccination, the statement is made that the death rate from smallpox in New York is 0.05 per 1,000 population as compared with 2.46 in Minnesota. This is an error, since the numbers quoted actually refer to the maximum annual incidence rates in the two states for the years from 1915 to 1920.

ATLAS DER HISTOTOPOGRAPHIE GESUNDER UND ERKRANKTER ORGANE. VON DR. ERWIN CHRISTELLER, Direktor der Pathologisch-Anatomischen Abteilung des Städtischen Rudolf Virchow-Krankenhauses in Berlin. Mit 182 direkten Photogrammen in Dreifarbendruck auf 88 Tafeln und 4 Textabbildungen. Price, bound, 90 marks. Leipzig: Georg Thieme, 1927.

In this valuable atlas, Christeller presents a variety of striking illustrations from large frozen sections. The technic, as he describes it, seems simple and practical enough to merit wide trial. The advantages of the method in diagnosis, in instruction of students and in investigation are obvious: large sections, extending across entire organs and stained in various ways, are available for macroscopic (topographic) as well as for microscopic study. The relations of structural elements and the extent and distribution of morbid changes, particularly, of course, the submacroscopic—for example, infectious foci, cellular emboli, and neoplastic metastases—are seen far better than in the gross or even in microscopic sections of the usual size. The atlas contains eighty-eight plates, with direct reproductions by a successful three color process of 182 photographs, explanatory text, and an introductory section on technical matters. The arrangement is most convenient: in all cases the explanation, which includes a brief statement of the clinical history and the condition found after death, occupies the page opposite the corresponding plate. The usual magnification of the histotopographic sections is only 1.5:1, which appears to answer well for topographic study, but in many cases the minute structure of selected small areas is shown under higher microscopic powers. The normal structure of many organs and a representative selection of the more common important morbid processes are illustrated, but the author has not attempted to include the whole field of morbid anatomy. The atlas is instructive and of interest to the student, the physician and the investigator.

Books Received

ARBEITEN AUS DEM STAATSIINSTITUT FÜR EXPERIMENTELLE THERAPIE UND DEM GEORG SPEYER-HAUSE ZU FRANKFURT A. M. Heft 19. R. Otto und H. Hetsch, Die Prüfung und Wertbemessung der Sera und Impfstoffe. Mit einer Einführung von W. Kolle und 6 Abbildungen im Text. Pp. 157. Jena: Gustav Fischer, 1927.

FIFTEENTH ANNUAL REPORT, MEDICAL DEPARTMENT, UNITED FRUIT COMPANY. Pp. 355. 1926.

ARBEITEN AUS DEM PATHOLOGISCHEN INSTITUT DER UNIVERSITÄT HELSINGFORS (FINLAND). Begründet von Prof. emer. Dr. E. A. Hönén Herausgegeben von Prof. Dr. Axel Wallgren. Neue Folge, IV Band. Mit 100 Abbildungen im Text und 7 Tafeln. Pp. 458. Jena: Gustav Fischer, 1926.

STANDARD METHODS OF THE DIVISION OF LABORATORIES AND RESEARCH OF THE NEW YORK STATE DEPARTMENT OF HEALTH. General Laboratory Procedures and the Methods used in the Department for the Preparation of Media and Glassware, the Laboratories for Sanitary and Analytical Chemistry, the Research, Publications, and Library Department, the Antitoxin, Serum, and Vaccine Laboratories, the Diagnostic Laboratories, the Executive Offices. Augustus B. Wadsworth, M.D., Director. Pp. 646, with 70 illustrations. Price, \$7.50. Baltimore: Williams & Wilkins Company, 1927.

TEXT-BOOK OF BACTERIOLOGY. By William W. Ford, M.D., Professor of Bacteriology, School of Hygiene and Public Health; Lecturer on Hygiene, School of Medicine, Johns Hopkins University. Octavo of 1,069 pages with 186 illustrations. Cloth. Price, \$8.50 net. Philadelphia: W. B. Saunders Company, 1927.

A TEXT-BOOK OF PATHOLOGY. By Alfred Stengel, M.D., Sc.D., Professor of Medicine, University of Pennsylvania, and Herbert Fox, M.D., Professor of Comparative Pathology, and Director of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania. Ed. 8, reset. Octavo of 1,138 pages with 552 text illustrations, many in colors, and 18 colored plates. Cloth. Price, \$10 net. Philadelphia: W. B. Saunders Company, 1927.

ATLAS DER HISTOTOPOGRAPHIE GESUNDER UND ERKRANKTER ORGANE. Von Dr. Erwin Christeller, Direktor der Pathologisch-Anatomischen Abteilung des Städtischen Rudolf Virchow-Krankenhauses in Berlin. Mit 182 direkten Photogrammen in Dreifarbendruck auf 88 Tafeln und 4 Textabbildungen. Price, bound, 90 marks. Leipzig: George Thieme, 1927.

SEGREGATION AND AUTOGAMY IN BACTERIA. A Contribution to Cellular Biology. By F. H. Stewart, M.A., D.Sc., M.D., Major, Indian Medical Service (Ret.). Pp. 104. Plates 4. Price, 7s. 6d. net. London: Adlard & Son, Limited, 1927.